

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 July 2005 (07.07.2005)

PCT

(10) International Publication Number
WO 2005/061505 A1

(51) International Patent Classification⁷: C07D 487/04,
A61K 31/4985, A61P 25/00 // (C07D 487/04, 239:00,
235:00)

(21) International Application Number:
PCT/IB2004/004019

(22) International Filing Date: 6 December 2004 (06.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/530,012 16 December 2003 (16.12.2003) US

(71) Applicant (for all designated States except US): PFIZER
PRODUCTS INC. [US/US]; Eastern Point Road, Groton,
CT 06340 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): CARPINO, Philip,
Albert [US/US]; Pfizer Global Research & Development,
Eastern Point Road, Groton, CT 06340 (US).

(74) Agent: FULLER, Grover, F., Jr.; c/o Lawrence, Jackie,
Pfizer Inc. MS8260-1615, Eastern Point Road, Groton, CT
06340 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

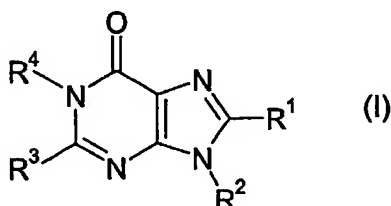
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC IMIDAZOLYL PYRIMIDIN-4-ONE CANNABINOID RECEPTOR LIGANDS AND USES THEREOF



(57) Abstract: Compounds of Formula (I) are described herein. The
compounds have been shown to act as cannabinoid receptor ligands
and are therefore useful in the treatment of diseases linked to the me-
diation of the cannabinoid receptors in animals.

BICYCLIC IMIDAZOLYL PYRIMIDIN-4-ONE AS CANNABINOID RECEPTOR LIGANDS AND USES THEREOF

FIELD OF THE INVENTION

5 The present invention relates to bicyclic imidazolyl pyrimidinone (e.g., 1,9-dihydro-purin-6-one) compounds as cannabinoid receptor ligands, in particular CB1 receptor antagonists, and uses thereof for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists.

BACKGROUND

10 Obesity is a major public health concern because of its increasing prevalence and associated health risks. Obesity and overweight are generally defined by body mass index (BMI), which is correlated with total body fat and estimates the relative risk of disease. BMI is calculated by weight in kilograms divided by height in meters squared (kg/m^2). Overweight is typically defined
15 as a BMI of 25-29.9 kg/m^2 , and obesity is typically defined as a BMI of 30 kg/m^2 . See, e.g., National Heart, Lung, and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, Washington, DC: U.S. Department of
20 Health and Human Services, NIH publication no. 98-4083 (1998).

The increase in obesity is of concern because of the excessive health risks associated with obesity, including coronary heart disease, strokes, hypertension, type 2 diabetes mellitus, dyslipidemia, sleep apnea, osteoarthritis, gall bladder disease, depression, and certain forms of cancer
25 (e.g., endometrial, breast, prostate, and colon). The negative health consequences of obesity make it the second leading cause of preventable death in the United States and impart a significant economic and psychosocial effect on society. See, McGinnis M, Foege WH., "Actual Causes of Death in the United States," JAMA, **270**, 2207-12 (1993).

30 Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Although weight loss is an important treatment outcome, one of the main goals of obesity management

is to improve cardiovascular and metabolic values to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations. Hence, it is believed that a 5-10%
5 intentional reduction in body weight may reduce morbidity and mortality.

Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. Satiety is achieved by increasing synaptic levels of norepinephrine, serotonin, or both. For example, stimulation of serotonin receptor subtypes
10 1B, 1D, and 2C and 1- and 2-adrenergic receptors decreases food intake by regulating satiety. See, Bray GA, "The New Era of Drug Treatment. Pharmacologic Treatment of Obesity: Symposium Overview," Obes Res., 3(suppl 4), 415s-7s (1995). Adrenergic agents (e.g., diethylpropion, benzphetamine, phendimetrazine, mazindol, and phentermine) act by
15 modulating central norepinephrine and dopamine receptors through the promotion of catecholamine release. Older adrenergic weight-loss drugs (e.g., amphetamine, methamphetamine, and phenmetrazine), which strongly engage in dopamine pathways, are no longer recommended because of the risk of their abuse. Fenfluramine and dexfenfluramine, both serotonergic
20 agents used to regulate appetite, are no longer available for use.

More recently, CB1 cannabinoid receptor antagonists/inverse agonists have been suggested as potential appetite suppressants. See, e.g., Amone, M., et al., "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors,"
25 Psychopharmacol., 132, 104-106 (1997); Colombo, G., et al., "Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716," Life Sci., 63, PL113-PL117 (1998); Simiand, J., et al., "SR141716, a CB1 Cannabinoid Receptor Antagonist, Selectively Reduces Sweet Food Intake in Marmoset," Behav. Pharmacol., 9, 179-181 (1998); and Chaperon, F., et
30 al., "Involvement of Central Cannabinoid (CB1) Receptors in the Establishment of Place Conditioning in Rats," Psychopharmacology, 135,

324-332 (1998). For a review of cannabinoid CB1 and CB2 receptor modulators, see Pertwee, R.G., "Cannabinoid Receptor Ligands: Clinical and Neuropharmacological Considerations, Relevant to Future Drug Discovery and Development," Exp. Opin. Invest. Drugs, 9(7), 1553-1571 (2000).

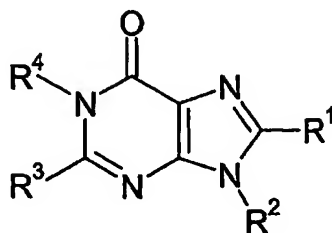
5 Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment for reducing or preventing weight-gain.

 In addition to obesity, there also exists an unmet need for treatment of alcohol abuse. Alcoholism affects approximately 10.9 million men and 4.4
10 million women in the United States. Approximately 100,000 deaths per year have been attributed to alcohol abuse or dependence. Health risks associated with alcoholism include impaired motor control and decision-making, cancer, liver disease, birth defects, heart disease, drug/drug interactions, pancreatitis and interpersonal problems. Studies have
15 suggested that endogenous cannabinoid tone plays a critical role in the control of ethanol intake. The endogenous CB1 receptor antagonist SR-141716A has been shown to block voluntary ethanol intake in rats and mice. See, Amone, M., et al., "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors,"
20 Psychopharmacol, 132, 104-106 (1997). For a review, see Hungund, B.L. and B.S. Basavarajappa, "Are Anandamide and Cannabinoid Receptors involved in Ethanol Tolerance? A Review of the Evidence," Alcohol & Alcoholism, 35(2) 126-133, 2000.

 Current treatments for alcohol abuse or dependence generally suffer
25 from non-compliance or potential hepatotoxicity; therefore, there is a high unmet need for more effective treatment of alcohol abuse/dependence.

SUMMARY

The present invention provides compounds of Formula (I):



(I)

wherein

R¹ is an aryl optionally substituted with one or more substituents, or a
5 heteroaryl optionally substituted with one or more substituents;

R² is aryl optionally substituted with one or more substituents,
heteroaryl optionally substituted with one or more substituents, -CH=CH-
R^{2a}, or -CH₂CH₂-R^{2a}, where R^{2a} is hydrogen or a chemical moiety selected
10 from (C₁-C₈)alkyl, 3- to 8-membered partially or fully saturated carbocyclic
ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl,
heteroaryl, where the chemical moiety is optionally substituted with one or
more substituents;

R³ is hydrogen, (C₁-C₄)alkyl, halo-substituted (C₁-C₄)alkyl, or (C₁-
C₄)alkoxy,

15 or R³ taken together with R⁴ forms a nitrogen containing 5- to 6-
membered partially or fully saturated heterocyclic ring optionally substituted
with one or more substituents; and

R⁴ is a chemical moiety selected from the group consisting of (C₁-
C₈)alkyl, aryl, heteroaryl, aryl(C₁-C₄)alkyl, a 3- to 8-membered partially or
20 fully saturated carbocyclic ring(s), heteroaryl(C₁-C₃)alkyl, 5-6 membered
lactone, 5- to 6-membered lactam, and a 3- to 8-membered partially or fully
saturated heterocycle, where said chemical moiety is optionally substituted
with one or more substituents,

or R⁴ taken together with R³ forms a nitrogen containing 5- to 6-
25 membered partially or fully saturated heterocyclic ring optionally substituted
with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

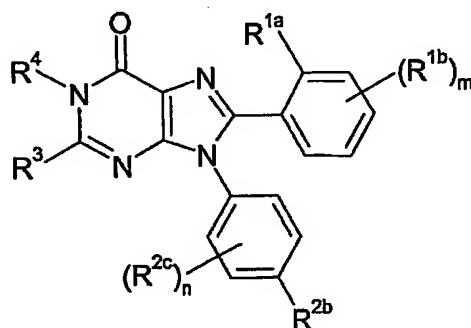
Preferably, R^1 and R^2 are each independently a substituted phenyl.

5 More preferably, R^1 and R^2 are each independently a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), (C_1-C_4) alkoxy, (C_1-C_4) alkyl, halo-substituted (C_1-C_4) alkyl (preferably fluoro-substituted alkyl, more preferably, trifluoromethyl) and cyano. Most preferably, R^1 is 2-cyanophenyl, 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl, 4-cyanophenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, or 4-fluorophenyl.

Preferably, R^3 is hydrogen, methyl or trifluoromethyl.

15 Preferably, R^4 is a chemical moiety selected from the group consisting of (C_1-C_8) alkyl, aryl (C_1-C_4) alkyl, and 3- to 8-membered partially or fully saturated carbocyclic ring(s), and 3- to 8-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituent. More preferably, R^4 is (C_1-C_8) alkyl, halo-substituted (C_1-C_8) alkyl (preferably, fluoro-substituted (C_1-C_8) alkyl),
20 cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl..

In a preferred embodiment of the present invention, a compound of Formula (II) is provided.



(II)

wherein

R^{1a} , R^{1b} , R^{2b} , and R^{2c} are each independently halo, (C₁-C₄)alkoxy, (C₁-C₄)alkyl, halo-substituted (C₁-C₄)alkyl, or cyano (preferably, R^{1a} is chloro, fluoro, methyl, or cyano; R^{1b} is chloro, fluoro or hydrogen (i.e., m is 0); R^{2b} is chloro, fluoro, (C₁-C₄)alkyl, trifluoromethyl, (C₁-C₄)alkoxy, or cyano; and R^{2c} is hydrogen (i.e., n is 0));

n and m are each independently 0, 1 or 2; and

R^3 and R^4 are as defined above;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferred compounds of Formula (I) or (II) include: 9-(4-chlorophenyl)-8-(2-chlorophenyl)-1-isopropyl-1,9-dihydropurin-6-one; 8-(2-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-9-(4-trifluoromethyl-phenyl)-1,9-dihydro-purin-6-one; 8-o-tolyl-1-(2,2,2-trifluoro-ethyl)-9-(4-trifluoromethyl-phenyl)-1,9-dihydro-purin-6-one; 8-(2-chloro-phenyl)-9-(4-ethyl-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one; 9-(4-tert-butyl-phenyl)-8-(2-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one; 4-[8-(2-chloro-phenyl)-6-oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-purin-9-yl]-benzonitrile; 2-[9-(4-chloro-phenyl)-6-oxo-1-(2,2,2-trifluoro-ethyl)-6,9-dihydro-1H-purin-8-yl]-benzonitrile; 9-(4-bromo-phenyl)-8-(2-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one; 8-(2-bromo-phenyl)-9-(4-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one; and 9-(4-chloro-phenyl)-8-(2-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one; or a solvate or hydrate of the compound.

Some of the compounds described herein may contain at least one chiral center; consequently, those skilled in the art will appreciate that all stereoisomers (e.g., enantiomers and diastereoisomers) of the compounds illustrated and discussed herein are within the scope of the present invention. In addition, tautomeric forms of the compounds are also within the scope of the present invention.

Compounds of the present invention have been shown to be useful cannabinoid receptor ligands (in particular, CB1 receptor antagonists). Accordingly, another aspect of the present invention is a pharmaceutical composition that comprises (1) a compound of the present invention, and (2)
5 a pharmaceutically acceptable excipient, diluent, or carrier. Preferably, the composition comprises a therapeutically effective amount of a compound of the present invention. The composition may also contain at least one additional pharmaceutical agent (described herein). Preferred agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone
10 and nalmeferene), dopaminergic agents (e.g., apomorphine), attention deficit disorder (ADD including attention deficit hyperactivity disorder (ADHD)) agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and anti-obesity agents (described herein below).

In yet another embodiment of the present invention, a method for
15 treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention (or a pharmaceutical composition thereof).

20 Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral
25 addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention
30 of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse

prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (ADD/ADHD), Parkinson's disease, and type II diabetes. In a preferred embodiment, the method is used in the treatment of weight loss, obesity, bulimia, ADD/ADHD, dementia, alcoholism, and/or tobacco abuse.

Compounds of the present invention may be administered in combination with other pharmaceutical agents. Preferred pharmaceutical agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmeferene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin™ and Concerta™), atomoxetine (e.g., Strattera™), and amphetamines (e.g., Adderall™)) and anti-obesity agents, such as apo-B/MTP inhibitors, 11 β -hydroxy steroid dehydrogenase-1 (11 β -HSD type 1) inhibitors, peptide YY₃₋₃₆ or analogs thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT_{2c} receptor agonists, melanin concentrating hormone receptor antagonists, leptin, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists (e.g., NPY Y5 antagonists such as those described hereinbelow), thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and the like.

The combination therapy may be administered as (a) a single pharmaceutical composition which comprises a compound of the present invention, at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two
5 separate pharmaceutical compositions comprising (i) a first composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier. The
10 pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1} . The alkane radical may be straight or branched.
15 For example, the term "(C₁-C₆)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of
20 an alkoxy, acyl (e.g., alkanoyl), alkylamino, dialkylamino, and alkylthio group have the same definition as above. When indicated as being "optionally substituted", the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or
25 perfluoroalkyls) independently selected from the group of substituents listed below in the definition for "substituted." "Halo-substituted alkyl" refers to an alkyl group substituted with one or more halogen atoms (e.g., "fluoro-substituted alkyl" refers to fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 2,2-difluoroethyl,
30 1,1,1-trifluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, 1,2,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,1,2-tetrafluoroethyl,

1,1,2,2,2-pentafluoroethyl, 1,1,1,2,2-pentafluoroethyl, perfluoroethyl, etc.). Preferred halo-substituted alkyls are the chloro- and fluoro-substituted alkyls, more preferably, fluoro-substituted alkyls. When substituted, the alkane radicals or alkyl moieties are preferably substituted with fluoro substituents (as described above), or 1 or 2 substituents independently selected from (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₂-C₃)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, cyano, hydroxy, (C₁-C₃)alkoxy, aryloxy, amino, (C₁-C₆)alkyl amino, di-(C₁-C₄)alkyl amino, aminocarboxylate (i.e., (C₁-C₃)alkyl-O-C(O)-NH-), hydroxy(C₂-C₃)alkylamino, or keto (oxo), and more preferably, 1 to 3 fluoro groups, or 1 substituent selected from (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₆)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, (C₁-C₃)alkoxy, (C₁-C₄)alkyl amino or di-(C₁-C₂)alkyl amino.

The terms "partially or fully saturated carbocyclic ring" (also referred to as "partially or fully saturated cycloalkyl") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the carbocyclic ring is generally a 3- to 8-membered ring. For example, partially or fully saturated carbocyclic rings (or cycloalkyl) include groups such as cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, norbornyl (bicyclo[2.2.1]heptyl), norbornenyl, bicyclo[2.2.2]octyl, and the like. When designated as being "optionally substituted", the partially saturated or fully saturated cycloalkyl group may be unsubstituted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted carbocyclic ring also includes groups wherein the carbocyclic ring is fused to a phenyl ring (e.g., indanyl). The carbocyclic group may be attached to the chemical entity or moiety by any one of the carbon atoms within the carbocyclic ring system. When substituted, the carbocyclic group is preferably substituted with 1 or 2 substituents independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₆)alkylidenyl,

aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C₁-C₃)alkoxy, aryloxy, amino, (C₁-C₆)alkyl amino, di-(C₁-C₄)alkyl amino, aminocarboxylate (i.e., (C₁-C₃)alkyl-O-C(O)-NH-), hydroxy(C₂-C₃)alkylamino, or keto (oxo), and more preferably 1 or 2 from substituents
5 independently selected from (C₁-C₂)alkyl, 3- to 6-membered heterocycle, fluoro, (C₁-C₃)alkoxy, (C₁-C₄)alkyl amino or di-(C₁-C₂)alkyl amino. Similarly, any cycloalkyl portion of a group (e.g., cycloalkylalkyl, cycloalkylamino, etc.) has the same definition as above.

The term "partially saturated or fully saturated heterocyclic ring" (also
10 referred to as "partially saturated or fully saturated heterocycle") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 6-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently
15 selected from sulfur, oxygen and/or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, N-methylpyrrolidinyl, imidazolidinyl, imidazoliny, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino,
20 thiomorpholino, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, and the like. When indicated as being "optionally substituted", the partially saturated or fully saturated heterocycle group may be unsubstituted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for
25 "substituted." A substituted heterocyclic ring includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, etc.). When substituted, the heterocycle group is preferably substituted with 1 or 2 substituents independently selected from
30 (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₂-C₄)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C₁-C₃)alkoxy,

aryloxy, amino, (C₁-C₆)alkyl amino, di-(C₁-C₃)alkyl amino, aminocarboxylate (i.e., (C₁-C₃)alkyl-O-C(O)-NH-), or keto (oxo), and more preferably with 1 or 2 substituents independently selected from (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₆)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, or fluoro.

- 5 The heterocyclic group may be attached to the chemical entity or moiety by any one of the ring atoms within the heterocyclic ring system. Similarly, any heterocycle portion of a group (e.g., heterocycle-substituted alkyl, heterocycle carbonyl, etc.) has the same definition as above.

- The term "aryl" or "aromatic carbocyclic ring" refers to aromatic
10 moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 10-membered aromatic carbocyclic ring(s). When indicated as being "optionally substituted", the aryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents)
15 independently selected from the group of substituents listed below in the definition for "substituted." Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.). When substituted, the aromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C₁-C₄)alkyl, (C₂-C₃)alkenyl, aryl,
20 heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C₁-C₄)alkoxy, aryloxy, amino, (C₁-C₆)alkyl amino, di-(C₁-C₃)alkyl amino, or aminocarboxylate (i.e., (C₁-C₃)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C₁-C₄)alkyl, chloro, fluoro, cyano, hydroxy, or (C₁-C₄)alkoxy. The aryl group may be
25 attached to the chemical entity or moiety by any one of the carbon atoms within the aromatic ring system. Similarly, the aryl portion (i.e., aromatic moiety) of an aroyl or aroyloxy (i.e., (aryl)-C(O)-O-) has the same definition as above.

- The term "heteroaryl" or "heteroaromatic ring" refers to aromatic
30 moieties containing at least one heteroatom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system

(e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, etc.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. When indicated as being "optionally substituted", the heteroaryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." When substituted, the heteroaromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C₁-C₄)alkyl, (C₂-C₃)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C₁-C₄)alkoxy, aryloxy, amino, (C₁-C₆)alkyl amino, di-(C₁-C₃)alkyl amino, or aminocarboxylate (i.e., (C₁-C₃)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C₁-C₄)alkyl, chloro, fluoro, cyano, hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkyl amino or di-(C₁-C₂)alkyl amino. The heteroaryl group may be attached to the chemical entity or moiety by any one of the atoms within the aromatic ring system (e.g., imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, or pyrid-6-yl). Similarly, the heteroaryl portion (i.e., heteroaromatic moiety) of a heteroaryl or heteroaryloxy (i.e., (heteroaryl)-C(O)-O-) has the same definition as above.

The term "acyl" refers to hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C₁-C₆)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, t-butylacetyl, etc.), (C₃-C₆)cycloalkylcarbonyl (e.g.,

cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrrolyl-2-carbonyl, 1H-pyrrolyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions above. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "substituted" specifically envisions and allows for one or more substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Suitable substituents for any of the groups defined above include (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₆)alkenyl, (C₁-C₆)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, (C₁-C₆)alkoxy, aryloxy, sulfhydryl (mercapto), (C₁-C₆)alkylthio, arylthio, amino, mono- or di-(C₁-C₆)alkyl amino, quaternary ammonium salts, amino(C₁-C₆)alkoxy, aminocarboxylate (i.e., (C₁-C₆)alkyl-O-C(O)-NH-), hydroxy(C₂-C₆)alkylamino, amino(C₁-C₆)alkylthio, cyanoamino, nitro, (C₁-C₆)carbamyl, keto (oxo), acyl, (C₁-C₆)alkyl-CO₂-, glycolyl, glycylyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thio(C₁-C₆)alkyl-C(O)-, thio(C₁-C₆)alkyl-CO₂-, and combinations thereof. In the case of substituted combinations, such as "substituted aryl(C₁-C₆)alkyl", either the aryl or the

alkyl group may be substituted, or both the aryl and the alkyl groups may be substituted with one or more substituents (typically, one to three substituents except in the case of perhalo substitutions). An aryl or heteroaryl substituted carbocyclic or heterocyclic group may be a fused ring (e.g., indanyl, dihydrobenzofuranyl, dihydroindolyl, etc.).

The term "solvate" refers to a molecular complex of a compound represented by Formula (I) or (II) (including prodrugs and pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular

disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

5 The term "animal" refers to humans (male or female), companion animals (e.g., dogs, cats and horses), food-source animals; zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry.

10 The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

 The terms "treating", "treat", or "treatment" embrace both preventative, i.e., prophylactic, and palliative treatment.

15 The terms "modulated by a cannabinoid receptor" or "modulation of a cannabinoid receptor" refers to the activation or deactivation of a cannabinoid receptor. For example, a ligand may act as an agonist, partial agonist, inverse agonist, antagonist, or partial antagonist.

20 The term "antagonist" includes both full antagonists and partial antagonists, as well as inverse agonists.

 The term "CB-1 receptor" refers to the G-protein coupled type 1 cannabinoid receptor.

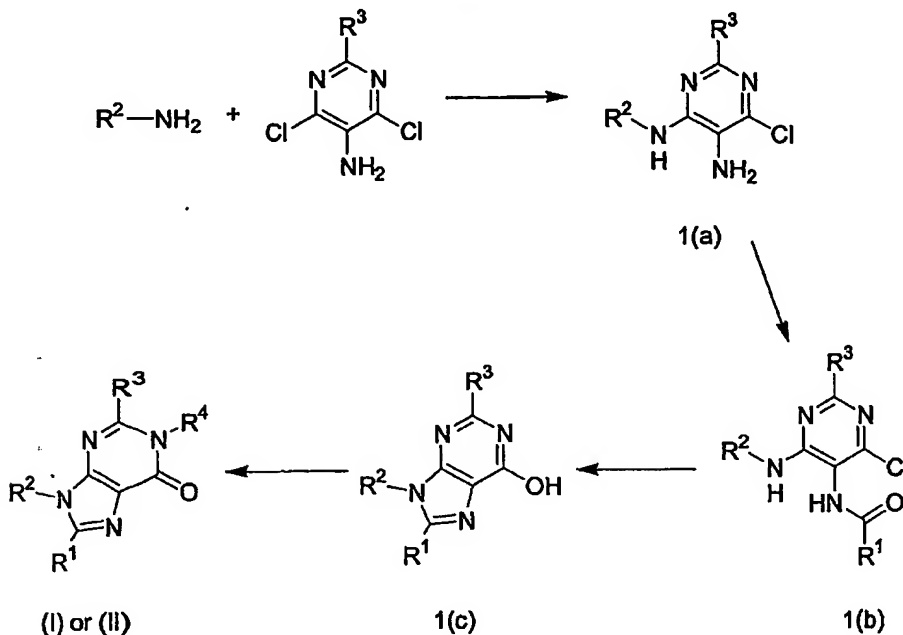
25 The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of Formulae (I) and (II), prodrugs thereof, pharmaceutically acceptable salts of the compounds, and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich
5 Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin,
10 including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will
15 appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods
20 described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the
25 nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenecarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of
30 protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of Formula (I) or (II) can be prepared using the general procedures described by R.J. Chorvat, et al. in J. Med. Chem., **42**, 833-848 (1999) and depicted in Scheme I below.



Scheme I

- Intermediate 1(a) where R³ is hydrogen may be prepared by reacting the desired amino compound (R²-NH₂, where R² is as defined above) with 4,6-dichloro-5-aminopyrimidine (available from Sigma-Aldrich, St. Louis, MO) in refluxing aqueous hydrochloric acid (A. Miyashita et al. in Chem. Pharm. Bull., **46**, 390-399 (1998)) or ethoxyethanol at elevated temperatures.
- Suitable amino compounds (R²-NH₂) include those compounds where R² is aryl (e.g., aniline) or substituted aryl (e.g., 2-chloroaniline, 2-fluoroaniline, 2,4-dichloroaniline, 2-fluoro-4-chloroaniline, 2-chloro-4-fluoroaniline, 2,4-difluoroaniline, and other substituted arylamines). Other commercially available derivatives of 4,6-dichloro-5-aminopyrimidine may be used as a starting material for those compounds of Formula (I) or (II) where R³ is other than hydrogen (e.g., 2-methyl-4,6-dichloro-5-aminopyrimidine and 2-ethyl-4,6-dichloro-5-aminopyrimidine). For representative literature syntheses of 4,6-dichloro-5-aminopyrimidine derivatives see: A. Albert et al. in J. Chem.

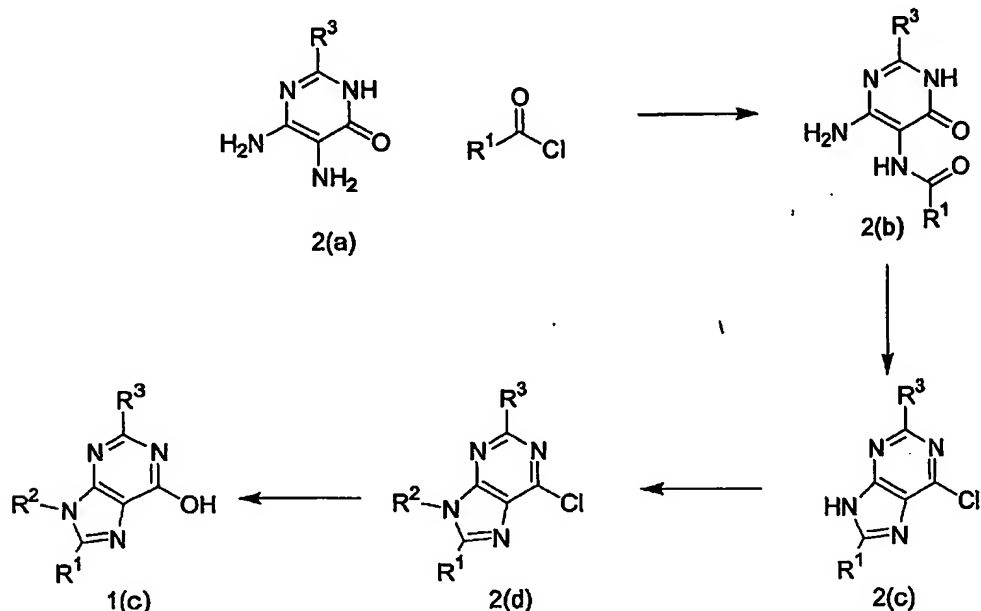
Soc., 3832 (1954) and W.E. Hymans in J. Heterocycl. Chem., **13**, 1141 (1976).

Intermediate 1(a) can then be acylated using conventional chemistry well-known to those skilled in the art. For example, intermediate 1(a) may
5 be reacted with the desired aroyl or heteroaroyle chloride in a basic solvent (e.g., pyridine) to produce intermediate 1(b). Alternatively, intermediate 1(a) may be reacted with the desired aroyl or heteroaroyle chloride in a reaction inert solvent (e.g., tetrahydrofuran, methylene chloride, *N,N*-dimethyl-
acetamide). The addition of a suitable base (e.g., triethylamine, diisopropyl-
10 ethylamine) may help facilitate the reaction. Suitable aroyl chlorides include benzoyl chloride, *o*-chlorobenzoyl chlorides, *o*-fluorobenzoyl chloride, *p*-chlorobenzoyl chloride, *p*-fluorobenzoyl chloride, 2,4-dichlorobenzoyl chloride, 2,4-difluorobenzoyl chloride, and the like.

Intermediate 1(b) may then be cyclized to the hydroxy purine (9H-
15 purin-6-ol) intermediate 1(c) by refluxing in a weak acid (e.g., acetic acid) or with sulfuric acid in an appropriate solvent (e.g., isopropyl alcohol, toluene).

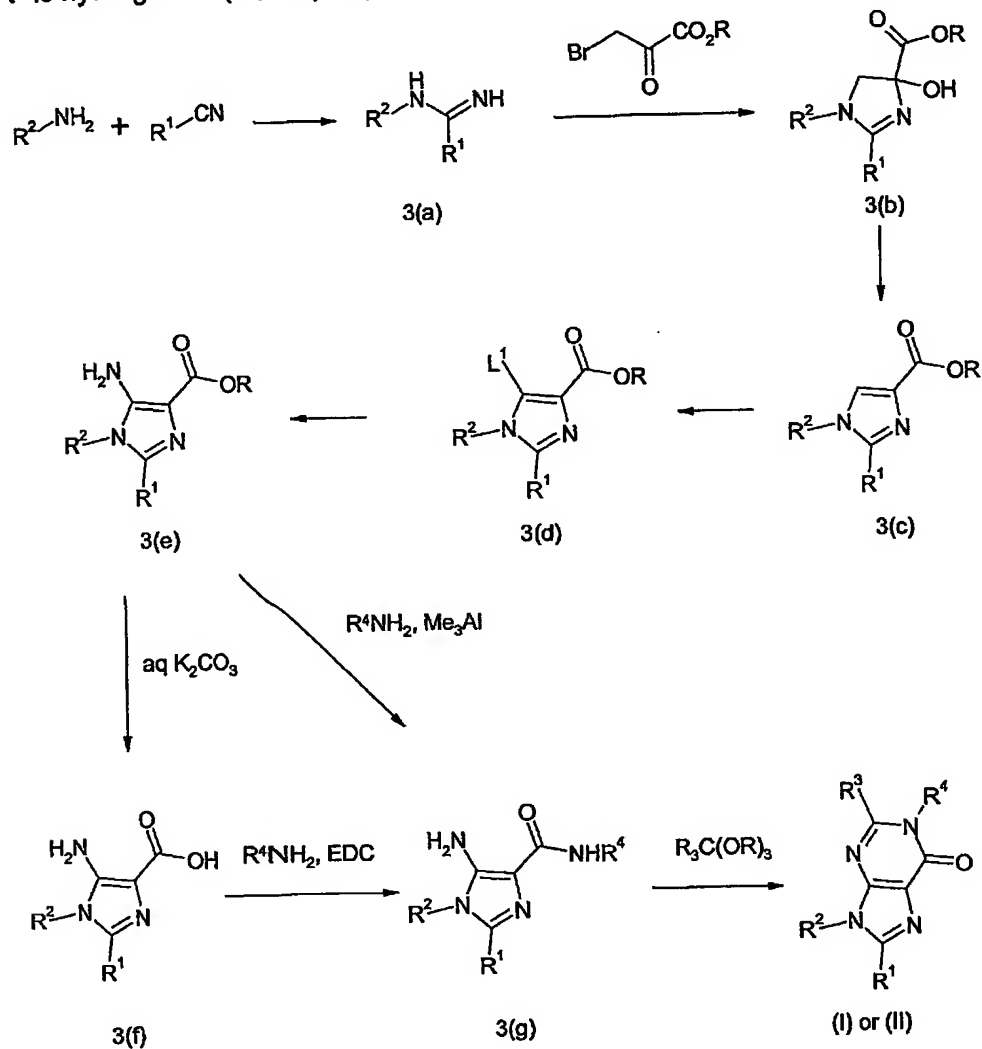
N-Alkylation of intermediate (1c) can then be accomplished using an alkylating agent, preferably an alkyl iodide, alkyl triflate, or a substituted benzyl bromide, and a base, such as lithium hexamethyldisilazide, cesium
20 carbonate, potassium carbonate or lithium hydride, in a polar non-protic solvent such as DMF or THF, at temperatures ranging from about 37°C to about 150 °C to provide compounds of Formula (I) or (II).

Scheme II below illustrates an alternative synthesis of intermediate 1(c).

**Scheme II**

Intermediate 2(a) can be first acylated with an acid chloride. Suitable acid chlorides (R¹-COCl) include those compounds where R¹ is aryl (e.g., benzoyl chloride), substituted aryl (e.g., 2-chlorobenzoyl chloride, 4-chlorobenzoyl chloride, and other substituted aryl acid chlorides), heteroaryl, or substituted heteroaryl. Compound 2(b) may be converted to intermediate 2(c) by treatment with dehydrating agents like POCl₃ using procedures described by H.C. Koppel in *J. Org. Chem.*, **23**, 1457 (1958) and in *J. Chem. Soc., Perkin Trans. I*, 879 (1984). The R¹ group, where R¹ is aryl, substituted aryl, heteroaryl or substituted heteroaryl, may then be introduced using reagents like R²-B(OH)₂, R²-Br or R²-I and Pd catalysts (see Y. Wan *et al.* in *Synthesis*, 1597-1600 (2002), and references contained therein) or copper(II) catalysts such as cupric acetate or cupric bromide (see, S. Ding *et al.* in *Tetrahedron Lett.*, **42**, 8751-8755 (2001), A. Klapars *et al.* *J. Am. Chem. Soc.* **123**, 7727-7729 (2001), and references contained therein). A S_NAr reaction may also be useful for introducing electron deficient heterocycles (see M. Medebielle in *New. J. Chem.*, **19**, 349 (1995)).

Scheme III describes the preparation of compounds of formula (I) or (II) where R^4 is alkyl, cycloalkyl, piperidiny, pyrrolidiny, aryl or heteroaryl and R^3 is hydrogen or (C₁-C₄) alkyl.



Scheme III

Intermediate 3(a) can be prepared by treating an appropriately substituted amine derivative (e.g., R^2NH_2) with trimethylaluminum under inert atmospheric conditions, followed by condensation with the appropriately substituted R^1CN derivative. Suitable amines include substituted phenyl amines (e.g., 4-chlorophenyl amine, 4-fluorophenyl amine, 4-bromophenyl amine, 4-iodophenyl amine, 4-cyanophenyl amine, and the like) pyridin-2-yl

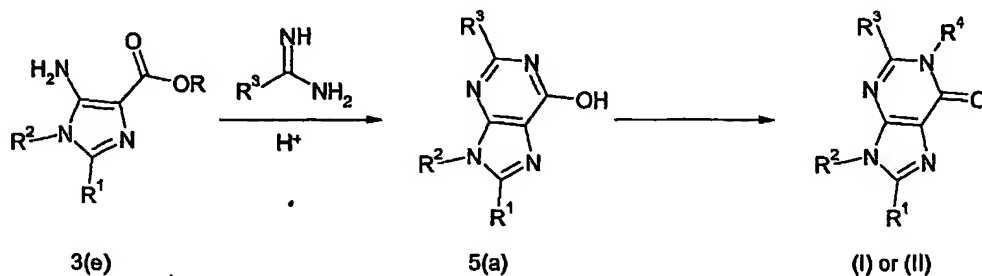
amine, pyridin-3-yl amine, pyridin-4-yl amine, substituted pyridinyl amines (e.g., 2-dimethylaminopyridin-5-yl amine, 2-methoxypyridin-5-yl amine, 5-chloropyridin-2-yl amine, 5-methylpyridin-2-yl, 5-methoxypyridin-2-yl amine, 3-chloropyridin-4-yl; amine, 2-N-morpholinylpyridin-5-yl, and the like), and
5 other commercially available or easily synthesized substituted or unsubstituted aryl and heteroaryl amines. Suitable cyano compounds include substituted benzonitriles (e.g., 2-chlorobenzonitrile, 2-fluorobenzonitrile, 2-methoxybenzonitrile, 2-methylbenzonitrile, 2,4-dichlorobenzonitrile, 2,4-difluorobenzonitrile, 2-chloro-4-fluorobenzonitrile, 2-chloro-4-methylbenzonitrile, 2,4-dimethoxybenzonitrile, 2-methyl-4-
10 chlorobenzonitrile, and the like), cyano-substituted pyridines (e.g., 4-cyano-3-chloropyridine) and other commercially available or easily synthesized substituted or unsubstituted aryl or heteroaryl nitriles.

Intermediate 3(a) can then be condensed with a 3-bromo-2-oxo-
15 propionic acid ester (wherein R is an alkyl group like methyl, ethyl, propyl, benzyl, etc.) to produce the cyclized 4-hydroxy-4,5-dihydro-1H-imidazole ester 3(b) using procedures analogous to those described by Khanna, I.K., et al., in *J. Med. Chem.*, **40**, 1634 (1997). For example, the amidine intermediate 3(a) is refluxed in a polar solvent (e.g., isopropanol) in the
20 presence of a mild base (e.g., sodium bicarbonate). Generally, the reaction (i.e., cyclization followed by dehydration) proceeds directly to the desired imidazole ester intermediate 3(c). In some instances, it may be necessary to dehydrate the carbinol condensation product 3(b) with an acid catalyst (e.g., p-toluenesulfonic acid) in a non-polar solvent (e.g., toluene) at temperatures
25 ranging from room temperature to 150 °C to provide the desired imidazole ester 3(c). Alternatively, intermediate 3(b) may be treated with methanesulfonyl chloride in the presence of a base (e.g., triethylamine) to give 3(c).

Intermediate 3(d), where L¹ is a bromine or iodine) can be
30 synthesized from imidazole ester 3(c) using a halogenating agent such as bromine, N-bromosuccinimide, iodine, or N-iodosuccinimide in a suitable

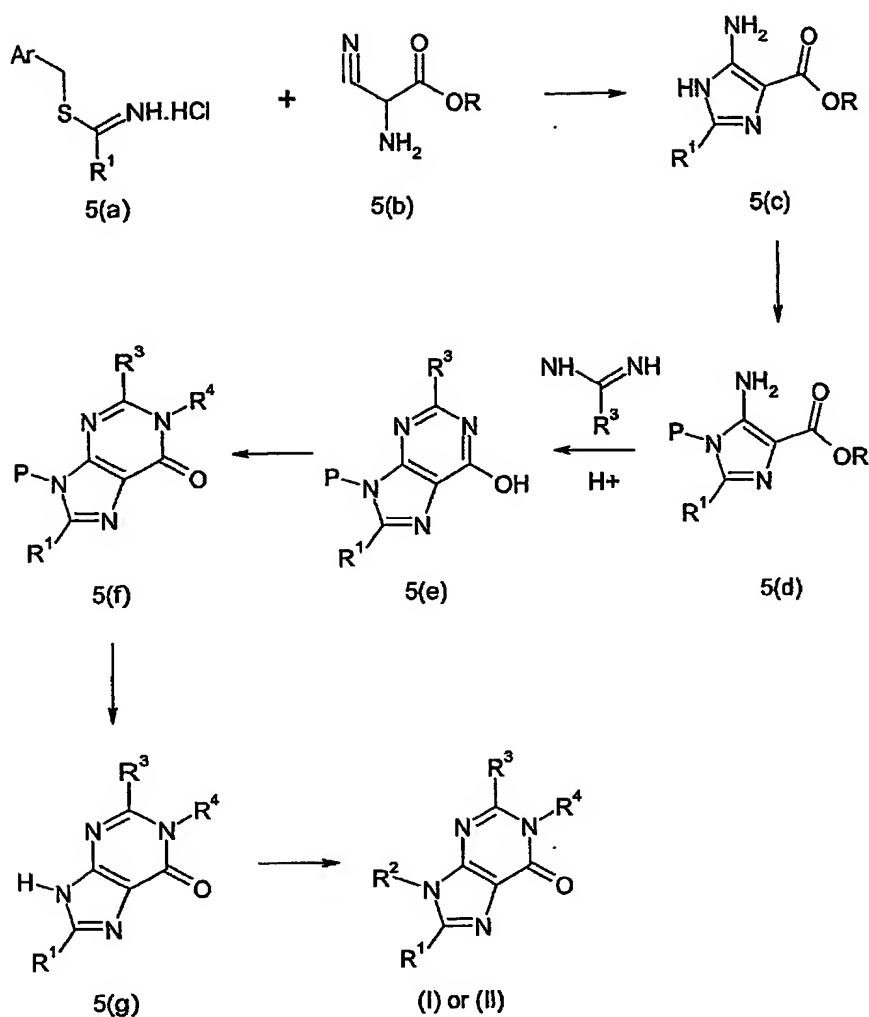
protic solvent (e.g., glacial acetic acid or trifluoroacetic acid) or an aprotic solvent (e.g., acetonitrile, ether or THF) at reaction temperatures ranging from 35 °C to 100 °C. The halogenated imidazolyl derivative 3(d) can be treated with an ammonia equivalent such as lithium bis(trimethylsilyl)amide in the presence of a catalytic amount of Pd(dba)₂ and a phosphine ligand such as P(t-Bu)₃ in a non-polar solvent (e.g., toluene) at temperatures ranging from 23 °C to reflux to give intermediate 3(e). Examples of related procedures are described by Lee et al. in Organic Letters, **3**, 2729-273 (2001). Hydrolysis of the carboxy-protecting group (R) in 3(e) with aqueous K₂CO₃ in an alcoholic solvent or with an alkali base such as KOH in a polar solvent (e.g., ethanol) can provide intermediate 3(f). Treatment of the acid 3(f) with an appropriately substituted cycloalkyl, aryl or heteroaryl amine (R⁴NH₂) in the presence of a coupling reagent (e.g., EDC or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)) and a base (e.g., triethylamine) in a suitable aprotic solvent (e.g., DMF, CH₂Cl₂) can provide intermediate 3(g). Alternatively, intermediate 3(e) can be directly treated with an appropriately substituted amine derivative (e.g., R⁴NH₂) in the presence of trimethylaluminum in a non-polar solvent (e.g., toluene) to give intermediate 3(g). Cyclocondensation of 3(g) with an ortho ester derivative (R³C(OR)₃) such as triethylorthoformate or triethylorthoacetate in the presence of an acid catalyst such as p-toluenesulfonic acid at temperatures ranging from about 50 °C to about 150 °C can provide compounds of Formula I or II.

The imidazolyl ester intermediate 3(e) can also be converted into compounds of formula (I) or (II) where R³ is not limited to hydrogen and C₁-C₄ alkyl by the methods shown in Scheme IV.

**Scheme IV**

Intermediate 3(a) can be reacted with an appropriately substituted amidine derivative in the presence of an acid catalyst (e.g., acetic acid) in a polar solvent (e.g., ethanol, 2-ethoxyethanol) to give the 9H-purin-6-ol intermediate 5(a) which can be N-alkylated as previously described to give compounds of formula (I) or (II).

Scheme V illustrates another method for preparing compounds of formula (I) or (II) where R² is aryl or heteroaryl.

**Scheme V**

An appropriately substituted thiobenzimidic acid benzyl ester 5(a) can be reacted with amino-cyano-acetic acid alkyl ester 5(b) in non-polar solvents (e.g. $CHCl_3$) to give the imidazolyl intermediate 5(c) (see J. Heyes, N. Ward in DE2142831). Protection of the imidazolyl group using methods well known in the art can provide intermediate 5(d). For example, 5(c) can be treated with benzyl bromide or p-methoxybenzyl bromide in an aprotic polar solvent (e.g. DMF) in the presence of a base (e.g., K_2CO_3) to give 5(d). Cyclocondensation of 5(d) can be accomplished as previously described using $R^3C(OR)_3$ to provide the 9H-purin-6-ol derivative 5(e). Reaction of 5(e) with R^4-L where L is a leaving group (e.g., Br, Cl, OTf) in the presence

of a base (e.g., Cs_2CO_3 or lithium hexamethyldisilazide) in a polar solvent (e.g., DMF or THF) can give the N-alkylated 1,9-dihydro-purin-6-one 5(f). Removal of the protecting group in 5(f) by standard methods well known in the art can provide 5(g). Intermediate 5(g) can be treated with substituted
5 arylboronic acids and Pd catalysts or aryl iodides (or arylbromides) and Cu catalysts as previously described to provide N-arylated compounds of formula (I) or (II).

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the
10 compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography),
15 recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compounds of the present invention may be isolated and used *per se* or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "salts" refers to inorganic and organic salts of a compound of the present invention. These salts can be prepared *in situ*
20 during the final isolation and purification of a compound, or by separately reacting the compound, N-oxide, or prodrug with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitate, pamoate,
25 malonate, stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium,
30 lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not

limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, e.g., Berge, et al., *J. Pharm. Sci.*, **66**, 1-19 (1977).

The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

Similarly, if a compound of the present invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-

C₄)alkanoyl, arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of the present invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇)cycloalkyl, benzyl, or R-carbonyl is a natural α -aminoacyl or natural α -aminoacyl-natural α -aminoacyl, -C(OH)C(O)OY' wherein Y' is H, (C₁-C₆)alkyl or benzyl, -C(OY₀)Y₁ wherein Y₀ is (C₁-C₄) alkyl and Y₁ is (C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl, -C(Y₂)Y₃ wherein Y₂ is H or methyl and Y₃ is mono-N- or di-N,N-(C₁-C₆)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

The compounds of the present invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the present invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the

diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also
5 be separated by use of a chiral HPLC column.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

10 It is also possible that the compounds of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic
15 tautomers) include interconversions *via* migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for
20 the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C ,
25 ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , and ^{36}Cl , respectively.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and
30 detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater

metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the
5 Schemes and/or in the Examples hereinbelow, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Compounds of the present invention are useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists; therefore, another embodiment of the present invention is a pharmaceutical
10 composition comprising a therapeutically effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and
15 excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is
20 being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol,
25 polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other
30 known additives to provide an elegant presentation of the drug (i.e., a

compound of the present invention or pharmaceutical composition thereof
or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and
mixing procedures. For example, the bulk drug substance (i.e., compound of
5 the present invention or stabilized form of the compound (e.g., complex with
a cyclodextrin derivative or other known complexation agent)) is dissolved in
a suitable solvent in the presence of one or more of the excipients described
above. The compound of the present invention is typically formulated into
pharmaceutical dosage forms to provide an easily controllable dosage of the
10 drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may
be packaged in a variety of ways depending upon the method used for
administering the drug. Generally, an article for distribution includes a
container having deposited therein the pharmaceutical formulation in an
15 appropriate form. Suitable containers are well-known to those skilled in the
art and include materials such as bottles (plastic and glass), sachets,
ampoules, plastic bags, metal cylinders, and the like. The container may
also include a tamper-proof assemblage to prevent indiscreet access to the
contents of the package. In addition, the container has deposited thereon a
20 label that describes the contents of the container. The label may also
include appropriate warnings.

The present invention further provides a method of treating diseases,
conditions and/or disorders modulated by cannabinoid receptor antagonists
in an animal that includes administering to an animal in need of such
25 treatment a therapeutically effective amount of a compound of the present
invention or a pharmaceutical composition comprising an effective amount of
a compound of the present invention and a pharmaceutically acceptable
excipient, diluent, or carrier. The method is particularly useful for treating
diseases, conditions and/or disorders modulated by cannabinoid receptor (in
30 particular, CB1 receptor) antagonists.

Preliminary investigations have indicated that the following diseases, conditions, and/or disorders are modulated by cannabinoid receptor antagonists: eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (ADD including attention deficit hyperactivity disorder (ADHD)), Parkinson's disease, and type II diabetes.

Accordingly, the compounds of the present invention described herein are useful in treating diseases, conditions, or disorders that are modulated by cannabinoid receptor antagonists. Consequently, the compounds of the present invention (including the compositions and processes used therein) may be used in the manufacture of a medicament for the therapeutic applications described herein.

Other diseases, conditions and/or disorders for which cannabinoid receptor antagonists may be effective include: premenstrual syndrome or late luteal phase syndrome, migraines, panic disorder, anxiety, post-traumatic syndrome, social phobia, cognitive impairment in non-demented individuals, non-amnestic mild cognitive impairment, post operative cognitive

decline, disorders associated with impulsive behaviours (such as, disruptive behaviour disorders (e.g., anxiety/depression, executive function improvement, tic disorders, conduct disorder and/or oppositional defiant disorder), adult personality disorders (e.g., borderline personality disorder and antisocial personality disorder), diseases associated with impulsive behaviours (e.g., substance abuse, paraphilias and self-mutilation), and impulse control disorders (e.g., intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania)), obsessive compulsive disorder, chronic fatigue syndrome, sexual dysfunction in males (e.g., premature ejaculation), sexual dysfunction in females, disorders of sleep (e.g., sleep apnea), autism, mutism, neurodegenerative movement disorders, spinal cord injury, damage of the central nervous system (e.g., trauma), stroke, neurodegenerative diseases or toxic or infective CNS diseases (e.g., encephalitis or meningitis), cardiovascular disorders (e.g., thrombosis), and diabetes.

The compounds of the present invention can be administered to a patient at dosage levels in the range of from about 0.7 mg to about 7,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of from about 0.01 mg to about 100 mg per kilogram body weight is typically sufficient. However, some variability in the general dosage range may be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular compound being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure. It is also noted that the compounds of the present invention can be used in sustained release, controlled release, and delayed release formulations, which forms are also well known to one of ordinary skill in the art.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that

include administering compounds of the present invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, 5 11 β -hydroxy steroid dehydrogenase-1 (11 β -HSD type 1) inhibitors, peptide YY₃₋₃₆ or analogs thereof, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine 10 agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT_{2c} agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y receptor 15 antagonists (e.g., NPY Y5 receptor antagonists, such as the spiro compounds described in US Patent Nos. 6,566,367; 6,649,624; 6,638,942; 6,605,720; 6,495,559; 6,462,053; 6,388,077; 6,335,345; and 6,326,375; US Publication Nos. 2002/0151456 and 2003/036652; and PCT Publication Nos. WO 03/010175. WO 03/082190 and WO 02/048152), thyromimetic agents, 20 dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), 25 ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

30 Especially preferred are anti-obesity agents selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin,

pseudoephedrine, PYY₃₋₃₆ or an analog thereof, and 2-oxo-N-(5-phenylpyrazinyl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

5 Representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the invention can be prepared using methods known to one of ordinary skill in the art, for example, sibutramine can be prepared as described in U.S. Pat. No. 4,929,629; bromocriptine can be prepared as described in U.S. Pat. Nos. 3,752,814 and
10 3,752,888; orlistat can be prepared as described in U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874; PYY₃₋₃₆ (including analogs thereof) can be prepared as described in US Publication No. 2002/0141985 and WO 03/027637; and the NPY Y5 receptor antagonist 2-oxo-N-(5-phenylpyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide can
15 be prepared as described in US Publication No. 2002/0151456. Other useful NPY Y5 receptor antagonists include those described in PCT Publication No. 03/082190, such as 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H), 4'-piperidine]-1'-carboxamide; 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)-spiro[isobenzofuran-1(3H), 4'-piperidine]-1'-carboxamide; N-
20 [5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[isobenzofuran-1(3H), [4'-piperidine]-1'-carboxamide; *trans*-3'-oxo-N-(5-phenyl-2-pyrimidinyl)] spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; *trans*-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; *trans*-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-
25 benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; *trans*-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H), 1'-cyclohexane]-4'-carboxamide; *trans*-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H), 1'-cyclohexane]-4'-carboxamide; *trans*-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-
30 1(3H),1'-cyclohexane]-4'-carboxamide; *trans*-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; *trans*-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; *trans*-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and pharmaceutically acceptable salts and esters thereof. All of the above recited U.S. patents and publications are incorporated herein by reference.

Other suitable pharmaceutical agents that may be administered in combination with the compounds of the present invention include agents designed to treat tobacco abuse (e.g., nicotine receptor partial agonists, bupropion hydrochloride (also known under the tradename Zyban™) and nicotine replacement therapies), agents to treat erectile dysfunction (e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and agents to treat alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia™) and nalmefene), disulfiram (also known under the tradename Antabuse™), and acamprosate (also known under the tradename Campral™). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta-blockers, clonidine, carbamazepine, pregabalin, and gabapentin (Neurontin™). Treatment for alcoholism is preferably administered in combination with behavioral therapy including such components as motivational enhancement therapy, cognitive behavioral therapy, and referral to self-help groups, including Alcohol Anonymous (AA).

Other pharmaceutical agents that may be useful include antihypertensive agents; anti-inflammatory agents (e.g., COX-2 inhibitors); antidepressants (e.g., fluoxetine hydrochloride (Prozac™)); cognitive improvement agents (e.g., donepezil hydrochloride (Aircept™) and other acetylcholinesterase inhibitors); neuroprotective agents (e.g., memantine); antipsychotic medications (e.g., ziprasidone (Geodon™), risperidone (Risperdal™), and olanzapine (Zyprexa™)); insulin and insulin analogs (e.g.,

LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH₂; sulfonylureas and analogs thereof: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, Glypizide[®], glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; α 2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linoglinide, A-4166; glitazones: ciglitazone, Actos[®] (pioglitazone), englitazone, troglitazone, darglitazone, Avandia[®] (BRL49653); fatty acid oxidation inhibitors: clomoxir, etomoxir, α -glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; β -agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex: fenfluramine; vanadate and vanadium complexes (e.g., Naglivan[®]) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994, pramlintide (Symlin[™]), AC 2993, nateglinide, aldose reductase inhibitors (e.g., zopolrestat), glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, sodium-hydrogen exchanger type 1 (NHE-1) inhibitors and/or cholesterol biosynthesis inhibitors or cholesterol absorption inhibitors, especially a HMG-CoA reductase inhibitor, or a HMG-CoA synthase inhibitor, or a HMG-CoA reductase or synthase gene expression inhibitor, a CETP inhibitor, a bile acid sequesterant, a fibrate, an ACAT inhibitor, a squalene synthetase inhibitor, an anti-oxidant or niacin. The compounds of the present invention may also be administered in combination with a naturally occurring compound that acts to lower plasma cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, *Hoodia* plant extracts, and niacin.

The dosage of the additional pharmaceutical agent will also be generally dependent upon a number of factors including the health of the subject being treated, the extent of treatment desired, the nature and kind of

concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of an anti-obesity agent is in the range of from about 0.001 mg to about 100 mg per kilogram body weight of the individual per day, preferably from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular anti-obesity agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent is administered to a subject in need of such treatment, preferably in the form of a pharmaceutical composition. In the combination aspect of the invention, the compound of the present invention and at least one other pharmaceutical agent may be administered either separately or in the pharmaceutical composition comprising both. It is generally preferred that such administration be oral. However, if the subject being treated is unable to swallow, or oral administration is otherwise impaired or undesirable, parenteral or transdermal administration may be appropriate.

According to the methods of the invention, when a combination of a compound of the present invention and at least one other pharmaceutical agent are administered together, such administration can be sequential in time or simultaneous with the simultaneous method being generally preferred. For sequential administration, a compound of the present invention and the additional pharmaceutical agent can be administered in any order. It is generally preferred that such administration be oral. It is especially preferred that such administration be oral and simultaneous. When a compound of the present invention and the additional pharmaceutical agent are administered

sequentially, the administration of each can be by the same or by different methods.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent (referred to herein as a "combination") is preferably administered in the form of a pharmaceutical composition. Accordingly, a compound of the present invention or a combination can be administered to a patient separately or together in any conventional oral, rectal, transdermal, parenteral, (for example, intravenous, intramuscular, or subcutaneous) intracisternal, intravaginal, intraperitoneal, intravesical, local (for example, powder, ointment or drop), or buccal, or nasal, dosage form.

Compositions suitable for parenteral injection generally include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of microorganism contamination of the compositions can be accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about

by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, a compound of the present invention or a combination is admixed with at least one inert customary pharmaceutical excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders (e.g., starches, lactose, sucrose, mannitol, silicic acid and the like); (b) binders (e.g., carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like); (c) humectants (e.g., glycerol and the like); (d) disintegrating agents (e.g., agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, sodium carbonate and the like); (e) solution retarders (e.g., paraffin and the like); (f) absorption accelerators (e.g., quaternary ammonium compounds and the like); (g) wetting agents (e.g., cetyl alcohol, glycerol monostearate and the like); (h) adsorbents (e.g., kaolin, bentonite and the like); and/or (i) lubricants (e.g., talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and the like). In the case of capsules and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the compound of the present invention and/or the additional pharmaceutical agent in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The drug can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of the present invention or the combination, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame seed oil and the like), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the compound of the present invention or the combination, may further comprise suspending agents, e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal or vaginal administration preferably comprise suppositories, which can be prepared by mixing a compound of the present invention or a combination with suitable non-irritating excipients or carriers, such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ordinary room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity thereby releasing the active component(s).

Dosage forms for topical administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents may comprise ointments, powders, sprays and inhalants. The drugs are admixed under sterile condition with a pharmaceutically acceptable carrier, and any preservatives, buffers, or

propellants that may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also intended to be included within the scope of the present invention.

5 The following paragraphs describe exemplary formulations, dosages, etc. useful for non-human animals. The administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents can be effected orally or non-orally (e.g., by injection).

10 An amount of a compound of the present invention or combination of a compound of the present invention with an anti-obesity agent is administered such that an effective dose is received. Generally, a daily dose that is administered orally to an animal is between about 0.01 and about 1,000 mg/kg of body weight, preferably between about 0.01 and about 300 mg/kg of body weight.

15 Conveniently, a compound of the present invention (or combination) can be carried in the drinking water so that a therapeutic dosage of the compound is ingested with the daily water supply. The compound can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate (such as an aqueous solution of a water-soluble salt).

20 Conveniently, a compound of the present invention (or combination) can also be added directly to the feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the compound in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and mineral mixes such as are commonly employed in poultry feeds. A particularly effective carrier is the respective animal feed itself; that is, a small portion of such feed. The carrier facilitates
25 uniform distribution of the compound in the finished feed with which the premix is blended. Preferably, the compound is thoroughly blended into the
30

premix and, subsequently, the feed. In this respect, the compound may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of compound in the concentrate are capable of wide variation since the amount of the compound in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of compound.

High potency concentrates may be blended by the feed manufacturer with proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements, which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound of the present invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to ensure homogeneity.

If the supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the compound across the top of the dressed feed.

Drinking water and feed effective for increasing lean meat deposition and for improving lean meat to fat ratio are generally prepared by mixing a compound of the present invention with a sufficient amount of animal feed to provide from about 10^{-3} to about 500 ppm of the compound in the feed or water.

The preferred medicated swine, cattle, sheep and goat feed generally contain from about 1 to about 400 grams of a compound of the present invention (or combination) per ton of feed, the optimum amount for these animals usually being about 50 to about 300 grams per ton of feed.

The preferred poultry and domestic pet feeds usually contain about 1 to about 400 grams and preferably about 10 to about 400 grams of a compound of the present invention (or combination) per ton of feed.

For parenteral administration in animals, the compounds of the present invention (or combination) may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and
5 improvement in lean meat to fat ratio is sought.

In general, parenteral administration involves injection of a sufficient amount of a compound of the present invention (or combination) to provide the animal with about 0.01 to about 20 mg/kg/day of body weight of the drug. The preferred dosage for poultry, swine, cattle, sheep, goats and domestic
10 pets is in the range of from about 0.05 to about 10 mg/kg/day of body weight of drug.

Paste formulations can be prepared by dispersing the drug in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

15 Pellets containing an effective amount of a compound of the present invention, pharmaceutical composition, or combination can be prepared by admixing a compound of the present invention or combination with a diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be added to improve the pelleting
20 process.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, implants may also be made periodically
25 during the animal treatment period in order to maintain the proper drug level in the animal's body.

The present invention has several advantageous veterinary features. For the pet owner or veterinarian who wishes to increase leanness and/or trim unwanted fat from pet animals, the instant invention provides the means
30 by which this may be accomplished. For poultry, beef, and swine breeders,

utilization of the method of the present invention yields leaner animals that command higher sale prices from the meat industry.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England).

General Experimental Procedures

NMR spectra were recorded on a Varian Unity™ 400 (available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz for proton. Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; 2s, two singlets. Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Fisons™ Platform II Spectrometer (carrier gas: acetonitrile: available from Micromass Ltd, Manchester, UK). Chemical ionization mass spectra (CI) were obtained on a Hewlett-Packard™ 5989 instrument (ammonia ionization, PBMS: available from Hewlett-Packard Company, Palo Alto, CA). Electrospray ionization mass spectra (ES) were obtained on a Waters™ ZMD instrument (carrier gas: acetonitrile: available from Waters Corp., Milford, MA). Where the intensity of chlorine or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}\text{Cl}/^{37}\text{Cl}$ -containing ions and 1:1 for $^{79}\text{Br}/^{81}\text{Br}$ -containing ions) and the intensity of only the lower mass ion is given. In some cases only representative ^1H NMR peaks are given. MS peaks are reported for all

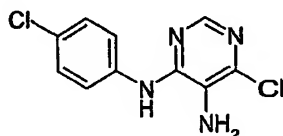
examples. Optical rotations were determined on a PerkinElmer™ 241 polarimeter (available from PerkinElmer Inc., Wellesley, MA) using the sodium D line ($\lambda = 589$ nm) at the indicated temperature and are reported as follows $[\alpha]_D^{\text{temp}}$, concentration ($c = \text{g}/100 \text{ ml}$), and solvent.

- 5 Column chromatography was performed with either Baker™ silica gel (40 μm ; J.T. Baker, Phillipsburg, NJ) or Silica Gel 50 (EM Sciences™, Gibbstown, NJ) in glass columns or in Flash 40 Biotage™ columns (ISC, Inc., Shelton, CT) under low nitrogen pressure.

10

Preparation of Key Intermediates

Preparation of Intermediate 6-Chloro-N4-(4-chlorophenyl)-pyrimidine-4,5-diamine (I-1A-1a):



I-1A-1a

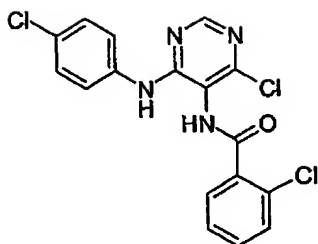
15

5-Amino-4,6-dichloropyrimidine (5.00 g, 29 mmol) and 4-chloroaniline (4.71 g, 36 mmol) were suspended in 80 ml H_2O and 12 ml ethanol. Concentrated HCl (1.2 ml, 14.5 mmol) was added at room temperature followed by warming reaction to 82 °C. After stirring for 19 hours, the reaction was cooled to room temperature and stirred for 60 hours. The precipitate was collected on a sintered glass funnel and rinsed with water followed by hexanes. After drying under vacuum, **I-1A-1a** was obtained as an off-white solid (7.38 g, 98%): +ESI MS ($M+1$) 255.3; ^1H NMR: (400 MHz, CD_3OD): δ 7.87 (s, 1H), 7.66 (d, $J = 8.7$ Hz, 2 H), 7.30 (d, $J = 8.7$ Hz, 2 H).

20

25

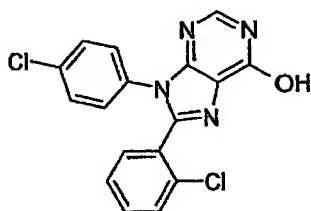
Preparation of Intermediate 2-Chloro-N-[4-chloro-6-(4-chlorophenylamino)-pyrimidin-5-yl]-benzamide (I-1A-1b):



1-1A-1b

6-Chloro-N4-(4-chlorophenyl)-pyrimidine-4,5-diamine 1-1A-1a (1.00 g, 3.92 mmol) was dissolved in 6 ml of *N,N*-dimethylacetamide giving a clear brown solution. After cooling to 5 °C, neat 2-chlorobenzoyl chloride (0.80 g, 4.34 mmol) was added over 1 minute. The solution was warmed to room temperature and stirred for 4 hours. Addition of water (15 ml) caused a white precipitate to come out of solution. The mixture was stirred for an additional 30 minutes at room temperature, then the precipitate was collected by vacuum filtration and rinsed with H₂O and then hexanes. The solid was further dried under vacuum to give 1-1A-1b as a colorless solid (1.27 g, 82%): +APCI MS (M+1) 393.1; ¹H NMR (400 MHz, DMSO-d₆) δ 10.02 (s, 1H), 9.11 (s, 1H), 8.40 (s, 1H), 7.93 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.66-7.40 (m, 7H).

Preparation of Intermediate 9-(4-Chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-ol (1-1A-1c-1):



1-1A-1c-1

To a suspension of 2-chloro-N-[4-chloro-6-(4-chlorophenylamino)-pyrimidin-5-yl]-benzamide 1-1A-1b (1.00 g, 2.54 mmol) in isopropanol (20 ml)

was added neat H₂SO₄ (410 µl, 7.4 mmol) at room temperature. The reaction was refluxed for 8 hours, followed by cooling to room temperature and stirring for 16 hours. To the heterogeneous solution was added 20 ml of water to promote further product precipitation. After stirring for an additional
5 hour at room temperature, the solid was collected on a sintered glass funnel and rinsed with water followed by hexanes. The product was further dried under reduced pressure to give I-1A-1c-1 as a colorless solid (0.72 g, 80%):
¹H NMR: (400 MHz, DMSO-d₆): δ 12.57 (s, 1H), 8.08 (d, *J* = 4.1 Hz, 1 H), 7.66 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.51-7.41 (m, 5H), 7.33-7.29 (m, 2H).

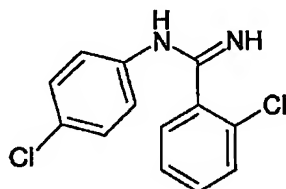
10

The following intermediate was prepared from the appropriately substituted aniline and benzoyl chloride derivatives by the procedures described above:

9-(4-Chloro-phenyl)-8-(2,4-dichloro-phenyl)-9H-purin-6-ol (I-1A-1c-2).

15

Preparation of Intermediate 2-Chloro-N-(4-chloro-phenyl)-benzamidine (I-1A-2a):



(I-1A-2a)

20

Trimethylaluminum (2M in hexanes, 100 ml, 200 mmol) was added dropwise to a solution of 4-chloro-phenylamine (18.2 g, 143 mmol) in toluene (550 ml) under a N₂ atmosphere at 0°C. The reaction mixture was warmed to room temperature and stirred for 3.5 hours. A solution of 2-chlorobenzonitrile (23.6 g, 171 mmol) in toluene (140 ml) was slowly added.

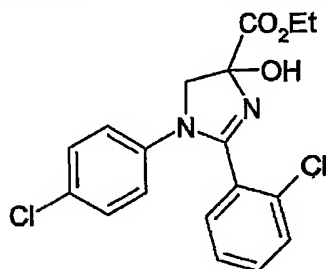
25

The heterogeneous mixture was heated at 80°C for 17 hours, cooled to room temperature, diluted with CHCl₃/methanol (2:1), and poured over a slurry of silica gel. The filter cake was washed with additional CH₂Cl₂/MeOH

(2:1). The combined filtrates were concentrated *in vacuo*, and the resulting yellow solid was triturated with hexanes/ether (2:1). The product, 2-chloro-N-(4-chloro-phenyl)-benzamidinium I-1A-2a, (25.1 g, 66%) was used without further purification.

5

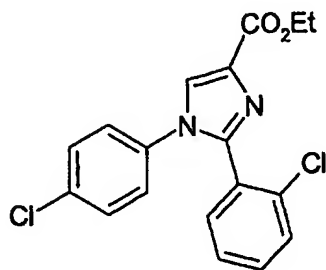
Preparation of Intermediate 1-(4-Chloro-phenyl)-2-(2-chloro-phenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (I-1A-2b):



(I-1A-2b)

10 A mixture of 2-chloro-N-(4-chloro-phenyl)-benzamidinium (I-1A-2a, 25.1 g, 95 mmol) and NaHCO₃ (84 g, 189 mmol) in 2-propanol (473 ml) was treated with 3-bromo-2-oxo-propionic acid ethyl ester (14.3 ml, 22 g, 113 mmol). The reaction mixture was heated at 80 °C for 17 hours. After cooling to room temperature, the solvent was removed *in vacuo*. The residue was diluted with CH₂Cl₂ and the organic solution was washed with H₂O, dried over MgSO₄, and concentrated *in vacuo* to provide the product, 1-(4-chloro-phenyl)-2-(2-chloro-phenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester I-1A-2b, as a dark red residue (36 g).

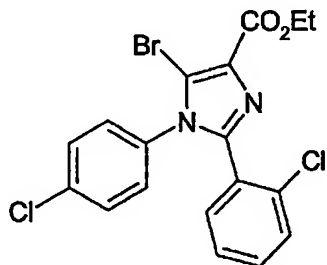
20 Preparation of 1-(4-Chloro-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (I-1A-2c):



(I-1A-2c)

The crude 1-(4-chlorophenyl)-2-(2-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (I-1A-2b, 36 g, 94.7 mmol) obtained from the previous step and *p*-toluenesulfonic acid monohydrate (4.5 g, 24 mmol) in toluene (630 ml) was heated under reflux for 17 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was taken up in CH₂Cl₂ and the organic solution was washed with H₂O, sat'd aq. NaHCO₃, and saturated aqueous NaCl, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by silica gel plug filtration using a solvent gradient of 2% EtOAc/CH₂Cl₂ to 10% EtOAc/CH₂Cl₂. The fractions containing the product were concentrated, and the oily residue was diluted with 1:3 EtOAc/hexanes (200 ml). After 1 hour, a solid precipitated out of solution and was collected by filtration to provide the product, 1-(4-chlorophenyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxylic acid ethyl ester I-1A-2c (18.63 g, 69.7%).

Preparation of 5-Bromo-1-(4-chlorophenyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxylic acid ethyl ester (I-1A-2d):

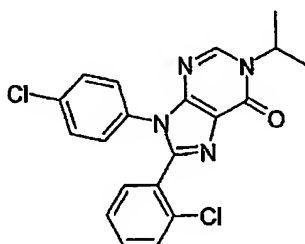


(I-1A-2d)

Bromine (3.6 ml, 0.07 mol) was added to a solution of 1-(4-chloro-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (1A-2c, 3.6 g, 0.01 mol) in glacial acetic acid (50 ml) at room temperature. The reaction mixture was stirred for 17 hours, poured over ice-water, and treated with 25% aqueous NaOH until a yellow color was formed. The aqueous solution was extracted with CH₂Cl₂ (3x), and the combined extracts were dried and concentrated *in vacuo* to give the desired compound, 5-bromo-1-(4-chloro-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester 1A-2d, as an oil (4.7 g): +APCI MS (M+1) 441.1; ¹H NMR (CD₃Cl) δ 1.41 (3H, t), 4.43 (2H, q), 7.08-7.12 (2H, m), 7.20 - 7.40 (7H, m).

Example 1

Preparation of 9-(4-Chlorophenyl)-8-(2-chlorophenyl)-1-isopropyl-1,9-dihydropurin-6-one (1A-1):



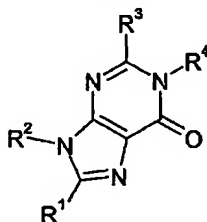
1A-1

9-(4-Chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-ol (1A-1c-1; 50 mg, 0.14 mmol), 2-iodopropane (26 mg, 0.15 mmol), and cesium carbonate (50 mg, 0.15 mmol) were combined in dimethylformamide (0.7 ml) and stirred overnight. Additional 2-iodopropane (13 mg, 0.76 mmol), and cesium carbonate (25 mg, 0.76 mmol) were added and stirred an additional day. The reaction mixture was diluted with ethyl ether and then washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried (Na₂SO₄), evaporated to dryness, and then purified on a Biotage™ Flash 12S column using 0-70% ethyl acetate in hexanes as eluant to afford title compound 1A-1 (30 mg, 53%); ¹H NMR: +ESI MS (M+1) 399.4; (400 MHz,

CD₂Cl₂) δ 8.07 (s, 1H), 7.54 (dd, J = 7.5, 1.2 Hz, 1H), 7.45-7.35 (m, 5H), 7.19 (d, J = 8.7 Hz, 2H), 5.28 (septuplet, J = 6.8 Hz, 1H), 1.49 (d, J = 7.1 Hz, 6H).

The compounds listed in Table 1 below were prepared using procedures analogous to those described above for the synthesis of Compound 1A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates. The compounds listed below were isolated initially as the free base and may be converted to their corresponding hydrochloride salt for testing.

Table 1



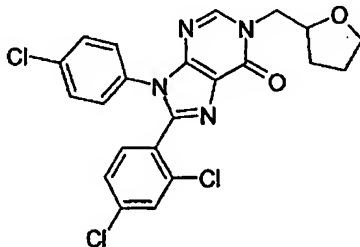
Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
1A-2	2-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CH ₃	419.2
1A-3	3-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CH ₃	419.2
1A-4	4-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CH ₃	419.2
1A-5	2-methyl-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CH ₃	399.3

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
1A-6	3-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	385.3
1A-7	4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	385.3
1A-8	2-methyl-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	365.3
1A-9	2-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH(CH ₃) ₂	433.4
1A-10	3-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH(CH ₃) ₂	433.4
1A-11	4-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH(CH ₃) ₂	433.4
1A-12	2-methyl-phenyl	4-trifluoro-methyl-phenyl	H	-CH(CH ₃) ₂	413.5
1A-13	3-chloro-phenyl	4-chloro-phenyl	H	-CH(CH ₃) ₂	399.4
1A-14	4-chloro-phenyl	4-chloro-phenyl	H	-CH(CH ₃) ₂	399.4
1A-15	2-methyl-phenyl	4-chloro-phenyl	H	-CH(CH ₃) ₂	379.4
1A-16	2-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CF ₃	473.4
1A-17	3-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CF ₃	473.4

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
1A-18	4-chloro-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CF ₃	473.4
1A-19	2-methyl-phenyl	4-trifluoro-methyl-phenyl	H	-CH ₂ CF ₃	453.5
1A-20	3-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	439.4
1A-21	2-methyl-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	419.4

Example 2

Preparation of 9-(4-Chlorophenyl)-8-(2,4-dichlorophenyl)-1-(tetrahydrofuran-2-ylmethyl)-1,9-dihydropurin-6-one (2A-1):

**2A-1**

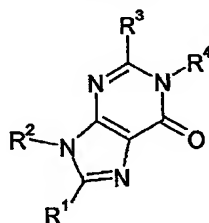
9-(4-Chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-ol (1-1A-1c-2, 100 mg, 0.255 mmol), 2-bromomethyl-tetrahydrofuran (42 mg, 0.255 mmol), and cesium carbonate (83 mg, 0.26 mmol) were combined in dimethylformamide (5 ml) and heated to 100 °C overnight. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous NaCl. The organic layer was dried (Na₂SO₄), filtered, and evaporated to dryness. The crude material was purified on a preparative TLC plate using 75% ethyl acetate/hexanes as the eluant to yield the title compound, 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-1-(tetrahydrofuran-2-ylmethyl)-1,9-

dihydropurin-6-one (2A-1; 100 mg, 82%): +APCI MS (M+1) 512.2; ^1H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.61 (d, 1H), 7.50 (s, 1H), 7.42 (d, 1H), 7.41 (d, 2H), 7.29 (d, 2H), 4.40 (d, 1H), 4.21 (d, 1H), 3.98 (m, 1H), 3.87 (m, 1H), 3.75 (m, 1H), 2.10 (m, 1H), 1.95 (m, 2H), 1.68 (m, 1H).

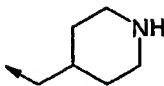
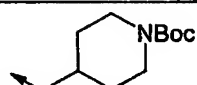
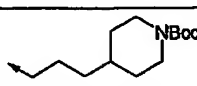
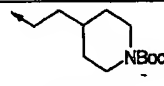
5 A solution of the above material in methylene chloride (~1 ml) was treated with 4 M HCl/dioxane (~0.5 ml), concentrated *in vacuo*, and dried under high vacuum to yield the hydrochloride salt of compound 2A-1: +APCI MS (M+1) 512.2.

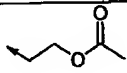
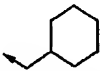

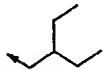










10 The compounds listed in Table 2 below were prepared using procedures analogous to those described above for the synthesis of Compound 2A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates. The compounds listed below were isolated initially as the free
15 base and then generally converted to their corresponding hydrochloride salt for testing.

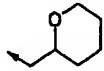

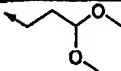



Table 2

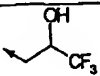
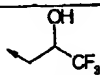
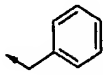
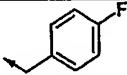



Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-2	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	419.1
2A-3	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CH ₃	433.2
2A-4	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CH ₂ CH ₃	447.2

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-5	2,4-dichloro-phenyl	4-chloro-phenyl	H	benzyl	481.2
2A-6	2,4-dichloro-phenyl	4-chloro-phenyl	H		488.2
2A-7	2,4-dichloro-phenyl	4-chloro-phenyl	H		588.3
2A-8	2,4-dichloro-phenyl	4-chloro-phenyl	H		616.3
2A-9	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₃	405.2
2A-10	2,4-dichloro-phenyl	4-chloro-phenyl	H		602.3
2A-11	4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	385.1
2A-12	4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CH ₃	399.1
2A-13	4-chloro-phenyl	2,4-dichloro-phenyl	H	-CH ₂ CH ₃	419.2
2A-14	4-chloro-phenyl	2,4-dichloro-phenyl	H	-CH ₂ CH ₂ CH ₃	433.2
2A-15	4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH(CH ₃) ₂	413.2
2A-16	4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CH ₃	399.1
2A-17	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH(CH ₃) ₂	447.1
2A-18	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CH ₃	433.2

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-19	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ N(CH ₃) ₂	462.2
2A-20	2,4-dichloro-phenyl	4-chloro-phenyl	H		477.2
2A-21	2,4-dichloro-phenyl	4-chloro-phenyl	H		487.2
2A-22	2,4-dichloro-phenyl	4-chloro-phenyl	H	cyclohexyl	473.2
2A-23	2,4-dichloro-phenyl	4-chloro-phenyl	H		461.2
2A-24	2,4-dichloro-phenyl	4-chloro-phenyl	H		475.2
2A-25	2,4-dichloro-phenyl	4-chloro-phenyl	H		445.2
2A-26	2,4-dichloro-phenyl	4-chloro-phenyl	H		447.2
2A-27	2,4-dichloro-phenyl	4-chloro-phenyl	H		461.2
2A-28	2,4-dichloro-phenyl	4-chloro-phenyl	H		431.2
2A-29	2,4-dichloro-phenyl	4-chloro-phenyl	H		461.2
2A-30	2,4-dichloro-phenyl	4-chloro-phenyl	H		475.1
2A-31	2,4-dichloro-phenyl	4-chloro-phenyl	H		445.2
2A-32	2,4-dichloro-phenyl	4-chloro-phenyl	H		449.2
2A-33	2,4-dichloro-phenyl	4-chloro-phenyl	H		461.2
2A-34	2,4-dichloro-phenyl	4-chloro-phenyl	H		477.1

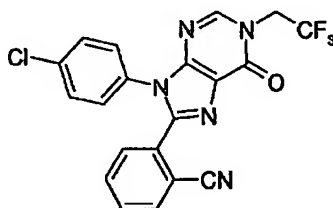
Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-35	2,4-dichloro-phenyl	4-chloro-phenyl	H		489.2
2A-36	2,4-dichloro-phenyl	4-chloro-phenyl	H		459.2
2A-37	2,4-dichloro-phenyl	4-chloro-phenyl	H		493.1
2A-38	2,4-dichloro-phenyl	4-chloro-phenyl	H		503.1
2A-39	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	473.1
2A-40	2-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	385.2
2A-41	2-chloro-phenyl	4-chloro-phenyl	H	-CH ₃	371.0
2A-42	2-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	439.1
2A-43	2,4-dichloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CF ₃	487.1
2A-44	2,4-dichloro-phenyl	4-chloro-phenyl	H	CH ₂ CH ₂ CH ₂ CF ₃	501.1
2A-45	2-chloro-phenyl	4-chloro-phenyl	H		469.1
2A-46	2-fluoro-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	403.2
2A-47	2-fluoro-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	457.1
2A-48	2-fluoro-4-chloro-phenyl	4-chloro-phenyl	H		487.1
2A-49	2-chloro-4-fluoro-phenyl	4-chloro-phenyl	H	-CH ₃	389.0
2A-50	2-chloro-4-fluoro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	403.2
2A-51	2-chloro-4-fluoro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	457.1

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-52	2-chloro-4-fluoro-phenyl	4-chloro-phenyl	H		487.1
2A-53	2-methyl-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₃	399.2
2A-54	2-methyl-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	453.1
2A-55	2-methyl-4-chloro-phenyl	4-chloro-phenyl	H		483.1
2A-56	2-chloro-4-fluoro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CF ₃	471.1
2A-57	2-methyl-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CF ₃	467.1
2A-58	2-fluoro-4-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CF ₃	471.1
2A-59	2-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CH ₂ CF ₃	453.1
2A-60	2-chloro-phenyl	4-chloro-phenyl	H		447.1
2A-61	2-chloro-phenyl	4-chloro-phenyl	H		465.1
2A-62	2-chloro-phenyl	4-chloro-phenyl	H		413.2
2A-63	2-chloro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	439.1
2A-64	2-chloro-phenyl	4-methoxy-phenyl	H	-CH ₂ CF ₃	435.0
2A-65	2-methyl-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	419.1
2A-66	2-fluoro-phenyl	4-methoxy-phenyl	H	-CH ₂ CF ₃	419.0
2A-67	2-bromo-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	484.8
2A-68	2-fluoro-phenyl	4-chloro-phenyl	H	-CH ₂ CF ₃	423.0
2A-69	2-chloro-phenyl	4-methyl-phenyl	H	-CH ₂ CF ₃	419.0

Example No.	R ¹	R ²	R ³	R ⁴	MS (M+H) ⁺
2A-70	2-chloro-phenyl	4-bromo-phenyl	H	-CH ₂ CF ₃	482.8
2A-71	2-chloro-phenyl	4- <i>t</i> -butyl-phenyl	H	-CH ₂ CF ₃	461.2
2A-72	2-chloro-phenyl	4-ethyl-phenyl	H	-CH ₂ CF ₃	433.2

Example 3

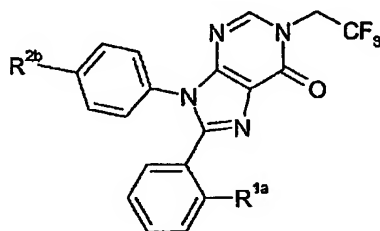
Preparation of 2-[9-(4-Chloro-phenyl)-6-oxo-1-(2,2,2-trifluoro-ethyl)-6,9-dihydro-1H-purin-8-yl]-benzonitrile (3A-1):

3A-1

A mixture of 8-(2-bromo-phenyl)-9-(4-chloro-phenyl)-1-(2,2,2-trifluoro-ethyl)-1,9-dihydro-purin-6-one (2A-67, 50 mg, 0.103 mmol), Zn(CN)₂ (18 mg, 0.155 mmol), Pd(PPh₃)₄ (12 mg, 0.01 mmol) in DMF (0.5 ml) was heated in a microwave apparatus (Emrys Optimizer, Personal Chemistry) at 200 °C for 3 minutes. The reaction mixture was quenched with sat'd aqueous NaCl and extracted with EtOAc (2x). The combined organic extracts were dried and concentrated under vacuum. The crude residue was purified via HPLC (Shimadzu) using a solvent gradient of 30% CH₃CN/hexanes to 100% CH₃CN to give the desired product 2-[9-(4-chloro-phenyl)-6-oxo-1-(2,2,2-trifluoro-ethyl)-6,9-dihydro-1H-purin-8-yl]-benzonitrile 3A-1 (20 mg): +APCI MS (M+1) 430.1; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.68 (d, 2H, J = 8.7 Hz), 7.62 (dd, 1H), 7.46 – 7.25 (m, 5H), 4.8 (q, 2H).

The compound listed in Table 3 below was prepared using procedures analogous to those described above for the synthesis of Compound 3A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates. The compound listed below was isolated initially as the free base and then generally converted to its corresponding hydrochloride salt for testing.

Table 3



Example No.	R ^{1a}	R ^{2b}	MS (M+H) ⁺
3A-2	Cl	CN	430.1

PHARMACOLOGICAL TESTING

The utility of the compounds of the present invention in the practice of the instant invention can be evidenced by activity in at least one of the protocols described hereinbelow. The following acronyms are used in the protocols described below.

BSA - bovine serum albumin

DMSO - dimethylsulfoxide

EDTA - ethylenediamine tetracetic acid

PBS – phosphate-buffered saline

EGTA - ethylene glycol-*bis*(β-aminoethyl ether) N,N,N',N'-tetraacetic acid

GDP - guanosine diphosphate

sc - subcutaneous

po - orally

ip - intraperitoneal

icv - intra cerebro ventricular

5 iv - intravenous

[³H]-SR141716A - tritiated N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride available from Amersham Biosciences, Piscataway, NJ.

10 [³H]-CP-55940 - radiolabeled 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol available from NEN Life Science Products, Boston, MA.

AM251 - N-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide available from Tocris™, Ellisville, MO.

15 Compounds having an activity <10 nM are generally tested in the CB1-R GTPγ [³⁵S] Binding Assay and the CB2-R binding assay described below in the Biological Binding Assays section. Selected compounds are then tested *in vivo* using one or more of the functional assays described in the Biological Functional Assays section below. The compounds provided a
20 range of binding activities from 0.5 to 5000 nM

In Vitro Biological Assays

Bioassay systems for determining the CB-1 and CB-2 receptor binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor
25 Ligands" Current Medicinal Chemistry, 6, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference).

The following assays were designed to detect compounds that inhibit the binding of [³H]-SR141716A (selective radiolabeled CB-1 ligand) and [³H]-
30 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol; radiolabeled CB-1/CB-2 ligand) to their respective receptors.

Rat CB-1 Receptor Binding Protocol

PelFreeze brains (available from Pel Freeze Biologicals, Rogers, Arkansas) were cut up and placed in tissue preparation buffer (5 mM Tris HCl, pH = 7.4 and 2 mM EDTA), polytroned at high speed and kept on ice
5 for 15 minutes. The homogenate was then spun at 1,000 X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000 X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris, pH = 7.4, 5 mM MgCl₂, and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the
10 assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [³H]-SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. A BCA protein assay was used to
15 determine the appropriate tissue concentration and then 200 µl of rat brain tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 20°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B
20 filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

Human CB-1 Receptor Binding Protocol

25 Human embryonic kidney 293 (HEK 293) cells transfected with the CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in homogenization buffer (10 mM EDTA, 10 mM EGTA, 10 mM Na bicarbonate, protease inhibitors; pH = 7.4), and homogenized with a Dounce Homogenizer. The homogenate was then spun at 1,000X g for 5
30 minutes at 4°C. The supernatant was recovered and centrifuged at 25,000X

G for 20 minutes at 4°C. The pellet was then re-suspended in 10 ml of homogenization buffer and re-spun at 25,000X G for 20 minutes at 4°C. The final pellet was re-suspended in 1 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM MgCl₂ and 1 mM EDTA). A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [³H]-SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

CB-2 Receptor Binding Protocol

Chinese hamster ovary-K1 (CHO-K1) cells transfected with CB-2 cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in tissue preparation buffer (5 mM Tris-HCl buffer (pH = 7.4) containing 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM MgCl₂ and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 10 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO, and 80.5% TME) and then 25 µl were added to the deep well polypropylene plate. [³H]-5-(1,1-Dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-

propyl)-cyclohexyl]-phenol was diluted in ligand buffer (0.5% BSA and 99.5% TME) and then 25 μ l of the solution were added to each well at a concentration of 1 nM. A BCA protein assay was used to determine the appropriate tissue concentration and 200 μ l of the tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 μ l of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron format onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. The filters were then counted on the Wallac Betaplate™ counter.

CB-1 Receptor GTP γ [³⁵S] Binding Assay

Membranes were prepared from CHO-K1 cells stably transfected with the human CB-1 receptor cDNA. Membranes were prepared from cells as described by Bass et al., in "Identification and characterization of novel somatostatin antagonists," *Molecular Pharmacology*, **50**, 709-715 (1996). GTP γ [³⁵S] binding assays were performed in a 96 well FlashPlate™ format in duplicate using 100 pM GTP γ [³⁵S] and 10 μ g membrane per well in assay buffer composed of 50 mM Tris HCl, pH 7.4, 3 mM MgCl₂, pH 7.4, 10 mM MgCl₂, 20 mM EGTA, 100 mM NaCl, 30 μ M GDP, 0.1 % bovine serum albumin and the following protease inhibitors: 100 μ g/ml bacitracin, 100 μ g/ml benzamidine, 5 μ g/ml aprotinin, 5 μ g/ml leupeptin. The assay mix was then incubated with increasing concentrations of antagonist (10^{-10} M to 10^{-5} M) for 10 minutes and challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (10 μ M). Assays were performed at 30°C for one hour. The FlashPlates™ were then centrifuged at 2000Xg for 10 minutes. Stimulation of GTP γ [³⁵S] binding was then quantified using a Wallac Microbeta. EC₅₀ calculations were performed using Prism™ by Graphpad.

Inverse agonism was measured in the absence of agonist using the protocol described above.

CB-1 Receptor FLIPR-based Functional Assay Protocol

CHO-K1 cells co-transfected with the human CB-1 receptor cDNA
5 (obtained from Dr. Debra Kendall, University of Connecticut) and the
promiscuous G-protein G16 were used for this assay. Cells were plated 48
hours in advance at 12500 cells per well on collagen coated 384 well black
clear assay plates. Cells were incubated for one hour with 4 μ M Fluo-4 AM
(Molecular Probes) in DMEM (Gibco) containing 2.5 mM probenecid and
10 pluronic acid (.04%). The plates were then washed 3 times with HEPES-
buffered saline (containing probenecid; 2.5 mM) to remove excess dye. After
20 min, the plates were added to the FLIPR individually and fluorescence
levels were continuously monitored over an 80 s period. Compound
additions were made simultaneously to all 384 wells after 20 s of baseline.
15 Assays were performed in triplicate and 6 point concentration-response
curves generated. Antagonist compounds were subsequently challenged
with 3 μ M WIN 55,212-2 (CB1-R agonist). Data were analyzed using Graph
Pad Prism.

Detection of Inverse Agonists

20 The following cyclic-AMP assay protocol using intact cells was used to
determine inverse agonist activity.

Cells were plated into a 96-well plate at a plating density of 10,000-
14,000 cells per well at a concentration of 100 μ l per well. The plates were
incubated for 24 hours in a 37°C incubator. The media was removed and
25 media lacking serum (100 μ l) was added. The plates were then incubated
for 18 hours at 37°C.

Serum free medium containing 1 mM IBMX was added to each well
followed by 10 μ l of test compound (1:10 stock solution (25 mM compound in
DMSO) into 50% DMSO/PBS) diluted 10X in PBS with 0.1% BSA. After
30 incubating for 20 minutes at 37°C, 2 μ M of Forskolin was added and then
incubated for an additional 20 minutes at 37°C. The media was removed,

100 μ l of 0.01N HCl was added and then incubated for 20 minutes at room temperature. Cell lysate (75 μ l) along with 25 μ l of assay buffer (supplied in FlashPlate™ cAMP assay kit available from NEN Life Science Products Boston, MA) into a Flashplate. cAMP standards and cAMP tracer were
5 added following the kit's protocol. The flashplate was then incubated for 18 hours at 4°C. The content of the wells were aspirated and counted in a Scintillation counter.

In Vivo Biological Assays

Cannabinoid agonists such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and
10 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol have been shown to affect four characteristic behaviors in mice, collectively known as the Tetrad. For a description of these behaviors see: Smith, P.B., et al. in "The pharmacological activity of anandamide, a putative
15 endogenous cannabinoid, in mice." J. Pharmacol. Exp. Ther., **270**(1), 219-227 (1994) and Wiley, J., et al. in "Discriminative stimulus effects of
anandamide in rats," Eur. J. Pharmacol., **276**(1-2), 49-54 (1995). Reversal of these activities in the Locomotor Activity, Catalepsy, Hypothermia, and Hot Plate assays described below provides a screen for *in vivo* activity of CB-1
receptor antagonists.

20 All data is presented as % reversal from agonist alone using the following formula: (5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol/agonist - vehicle/agonist)/(vehicle/vehicle - vehicle/agonist). Negative numbers indicate a potentiation of the agonist activity or non-antagonist activity. Positive numbers indicate a reversal of
25 activity for that particular test.

Locomotor Activity

Male ICR mice (n=6) (17-19 g, Charles River Laboratories, Inc.,
Wilmington, MA) were pre-treated with test compound (sc, po, ip, or icv).
Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-
30 2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc administration).
Twenty-five minutes after the agonist injection, the mice were placed in clear

acrylic cages (431.8 cm x 20.9 cm x 20.3 cm) containing clean wood shavings. The subjects were allowed to explore surroundings for a total of about 5 minutes and the activity was recorded by infrared motion detectors (available from Coulbourn Instruments™, Allentown, PA) that were placed
5 on top of the cages. The data was computer collected and expressed as "movement units."

Catalepsy

Male ICR mice (n=6,17-19 g upon arrival) were pre-treated with test compound (sc, po, ip or icv). Fifteen minutes later, the mice were
10 challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Ninety minutes post injection, the mice were placed on a 6.5 cm steel ring attached to a ring stand at a height of about 12 inches. The ring was mounted in a horizontal orientation and the mouse was suspended in the gap of the ring with fore- and hind-paws gripping the
15 perimeter. The duration that the mouse remained completely motionless (except for respiratory movements) was recorded over a 3-minute period.

The data were presented as a percent immobility rating. The rating was calculated by dividing the number of seconds the mouse remains motionless by the total time of the observation period and multiplying the
20 result by 100. A percent reversal from the agonist was then calculated.

Hypothermia

Male ICR mice (n=5) (17-19 g upon arrival) were pretreated with test compounds (sc, po, ip or icv). Fifteen minutes later, mice were challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-
25 hydroxy-propyl)-cyclohexyl]-phenol (sc). Sixty-five minutes post agonist injection, rectal body temperatures were taken. This was done by inserting a small thermostat probe approximately 2- 2.5 cm into the rectum.

Temperatures were recorded to the nearest tenth of a degree

Hot Plate

30 Male ICR mice (n=7,17-19 g upon arrival) are pre-treated with test compounds (sc, po, ip or iv). Fifteen minutes later, mice were challenged

with a cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc administration). Forty-five minutes later, each mouse was tested for reversal of analgesia using a standard hot plate meter (Columbus Instruments). The hot plate was 10" x 10" x 0.75" with a surrounding clear acrylic wall. Latency to kick, lick or flick hindpaw or jump from the platform was recorded to the nearest tenth of a second. The timer was experimenter activated and each test had a 40 second cut off. Data were presented as a percent reversal of the agonist induced analgesia.

Food Intake

The following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast.

Male Sprague-Dawley rats were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The rats were individually housed and fed powdered chow. They were maintained on a 12 hour light/dark cycle and received food and water *ad libitum*. The animals were acclimated to the vivarium for a period of one week before testing was conducted. Testing was completed during the light portion of the cycle.

To conduct the food intake efficacy screen, rats were transferred to individual test cages without food the afternoon prior to testing, and the rats were fasted overnight. After the overnight fast, rats were dosed the following morning with vehicle or test compounds. A known antagonist was dosed (3 mg/kg) as a positive control, and a control group received vehicle alone (no compound). The test compounds were dosed at ranges between 0.1 and 100 mg/kg depending upon the compound. The standard vehicle was 0.5% (w/v) methylcellulose in water and the standard route of administration was oral. However, different vehicles and routes of administration were used to accommodate various compounds when required. Food was provided to the rats 30 minutes after dosing and the Oxymax automated food intake system (Columbus Instruments, Columbus, Ohio) was started. Individual rat food intake was recorded continuously at 10-minute intervals for a period of two

hours. When required, food intake was recorded manually using an electronic scale; food was weighed every 30 minutes after food was provided up to four hours after food was provided. Compound efficacy was determined by comparing the food intake pattern of compound-treated rats to vehicle and the standard positive control.

Alcohol Intake

The following protocol evaluates the effects of alcohol intake in alcohol preferring (P) female rats (bred at Indiana University) with an extensive drinking history. The following references provide detailed descriptions of P rats: Li, T.-K., et al., "Indiana selection studies on alcohol related behaviors" in Development of Animal Models as Pharmacogenetic Tools (eds McClearn C. E., Deitrich R. A. and Erwin V. G.), Research Monograph 6, 171-192 (1981) NIAAA, ADAMHA, Rockville, MD; Lumeng, L., et al., "New strains of rats with alcohol preference and nonpreference" Alcohol And Aldehyde Metabolizing Systems, 3, Academic Press, New York, 537-544 (1977); and Lumeng, L., et al., "Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats," Pharmacol. Biochem Behav., 16, 125-130 (1982).

Female rats were given 2 hours of access to alcohol (10% v/v and water, 2-bottle choice) daily at the onset of the dark cycle. The rats were maintained on a reverse cycle to facilitate experimenter interactions. The animals were initially assigned to four groups equated for alcohol intakes: Group 1 – vehicle (n = 8); Group 2 – positive control (e.g. 5.6 mg/kg AM251; n = 8); Group 3 – low dose test compound (n = 8); and Group 4 – high dose of test compound (n = 8). Test compounds were generally mixed into a vehicle of 30% (w/v) β -cyclodextrin in distilled water at a volume of 1-2 ml/kg. Vehicle injections were given to all groups for the first two days of the experiment. This was followed by 2 days of drug injections (to the appropriate groups) and a final day of vehicle injections. On the drug injection days, drugs were given sc 30 minutes prior to a 2-hour alcohol access period. Alcohol intake for all animals was measured during the test period and a comparison was made

between drug and vehicle-treated animals to determine effects of the compounds on alcohol drinking behavior.

Additional drinking studies were done utilizing female C57BL/6 mice (Charles River). Several studies have shown that this strain of mice will readily consume alcohol with little to no manipulation required (Middaugh *et al.*, "Ethanol Consumption by C57BL/6 Mice: Influence of Gender and Procedural Variables" Alcohol, 17 (3), 175-183, 1999; Le *et al.*, "Alcohol Consumption by C57BL/6, BALA/c, and DBA/2 Mice in a Limited Access Paradigm" Pharmacology Biochemisrty and Behavior, 47, 375-378, 1994).

Mice (17-19 g) were individually housed upon arrival and given unlimited access to powdered rat chow, water and a 10 % (w/v) alcohol solution. After 2-3 weeks of unlimited access, water was restricted for 20 hours and alcohol was restricted to only 2 hours access daily. This was done in a manner that the access period was the last 2 hours of the dark part of the light cycle.

Once drinking behavior stabilized, testing commenced. Mice were considered stable when the average alcohol consumption for 3 days was \pm 20% of the average for all 3 days. Day 1 of test consisted of all mice receiving vehicle injection (sc or ip). Thirty to 120 minutes post injection, access was given to alcohol and water. Alcohol consumption for that day was calculated (g/kg) and groups were assigned (n=7-10) so that all groups had similar alcohol intake. On day 2 and 3, mice were injected with vehicle or drug and the same protocol as the previous day was followed. Day 4 was wash out and no injections were given. Data was analyzed using repeated measures ANOVA. Change in water or alcohol consumption was compared back to vehicle for each day of the test. Positive results would be interpreted as a compound that was able to significantly reduce alcohol consumption while having no effect on water

Oxygen Consumption

Methods:

Whole body oxygen consumption is measured using an indirect calorimeter (Oxymax from Columbus Instruments, Columbus, OH) in male Sprague Dawley rats. Rats (300-380 g body weight) are placed in the calorimeter chambers and the chambers are placed in activity monitors.

- 5 These studies are done during the light cycle. Prior to the measurement of oxygen consumption, the rats are fed standard chow ad libitum. During the measurement of oxygen consumption, food is not available. Basal pre-dose oxygen consumption and ambulatory activity are measured every 10 minutes for 2.5 to 3 hours. At the end of the basal pre-dosing period, the chambers
10 are opened and the animals are administered a single dose of compound (the usual dose range is 0.001 to 10 mg/kg) by oral gavage (or other route of administration as specified, i.e. s.c., i.p., i.v.). Drugs are prepared in methylcellulose, water or other specified vehicle (examples include PEG400, 30% beta-cyclo dextran and propylene glycol). Oxygen consumption and
15 ambulatory activity are measured every 10 minutes for an additional 1-6 hours post-dosing.

- The Oxymax calorimeter software calculates the oxygen consumption (ml/kg/h) based on the flow rate of air through the chambers and difference in oxygen content at inlet and output ports. The activity monitors have 15
20 infrared light beams spaced one inch apart on each axis, ambulatory activity is recorded when two consecutive beams are broken and the results are recorded as counts.

- Resting oxygen consumption, during pre- and post-dosing, is calculated by averaging the 10-min O₂ consumption values, excluding
25 periods of high ambulatory activity (ambulatory activity count > 100) and excluding the first 5 values of the pre-dose period and the first value from the post-dose period. Change in oxygen consumption is reported as percent and is calculated by dividing the post-dosing resting oxygen consumption by the pre-dose oxygen consumption *100. Experiments will typically be done
30 with n = 4-6 rats and results reported are mean +/- SEM.

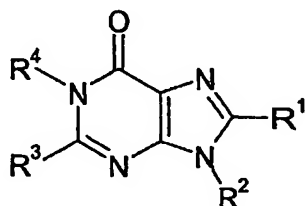
Interpretation:

An increase in oxygen consumption of >10% is considered a positive result. Historically, vehicle-treated rats have no change in oxygen consumption from pre-dose basal.

CLAIMS

What is claimed is:

1. A compound of Formula (I)



(I)

wherein

R¹ is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents;

- R² is aryl optionally substituted with one or more substituents,
10 heteroaryl optionally substituted with one or more substituents, $-\text{CH}=\text{CH}-\text{R}^{2a}$, or $-\text{CH}_2\text{CH}_2-\text{R}^{2a}$, where R^{2a} is hydrogen or a chemical moiety selected from (C₁-C₈)alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, heteroaryl, where said chemical moiety is optionally substituted with one or
15 more substituents;

R³ is hydrogen, (C₁-C₄)alkyl, halo-substituted (C₁-C₄)alkyl, or (C₁-C₄)alkoxy,

- or R³ taken together with R⁴ forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted
20 with one or more substituents; and

- R⁴ is a chemical moiety selected from the group consisting of (C₁-C₈)alkyl, aryl, heteroaryl, aryl(C₁-C₄)alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl(C₁-C₃)alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 8-membered partially or fully
25 saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said
5 compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

2. The compound of Claim 1 wherein R^4 is a chemical moiety selected from the group consisting of (C_1-C_8) alkyl, aryl(C_1-C_4)alkyl, 3- to 8-
10 membered partially or fully saturated carbocyclic ring(s), and 3- to 8-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

15

3. The compound of Claim 2 wherein R^3 is hydrogen, methyl or trifluoromethyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

20

4. The compound of Claim 2 wherein R^4 is (C_1-C_8) alkyl, fluoro-substituted (C_1-C_8) alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of
25 said compound or said salt.

5. The compound of Claim 3 wherein R^4 is (C_1-C_8) alkyl, fluoro-substituted (C_1-C_8) alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of
30 said compound or said salt.

6. The compound of Claim 1, 2, 3, 4 or 5 wherein R^1 and R^2 are each independently a substituted phenyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

5

7. The compound of Claim 6 wherein R^1 and R^2 are each independently a phenyl substituted with one to three substituents independently selected from the group consisting of halo, (C_1-C_4) alkoxy, (C_1-C_4) alkyl, halo-substituted (C_1-C_4) alkyl, and cyano;

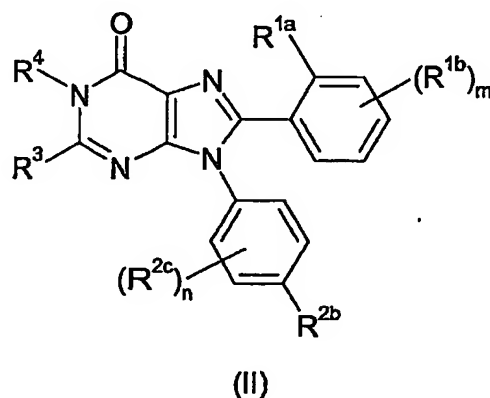
10 a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

8. The compound of Claim 7 wherein R^1 is 2-cyanophenyl, 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl or 2,4-difluorophenyl; and

15 R^2 is 4-chlorophenyl, 4-cyanophenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, or 4-fluorophenyl;

20 a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

9. A compound of Formula (II)



25

wherein

R^{1a} , R^{1b} , R^{2b} , and R^{2c} are each independently halo, (C₁-C₄)alkoxy, (C₁-C₄)alkyl, halo-substituted (C₁-C₄)alkyl, or cyano;

n and m are each independently 0, 1 or 2; and

5 R^3 is hydrogen, (C₁-C₄)alkyl, halo-substituted (C₁-C₄)alkyl, or (C₁-C₄)alkoxy,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

10 R^4 is a chemical moiety selected from the group consisting of (C₁-C₈)alkyl, aryl, heteroaryl, aryl(C₁-C₄)alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl(C₁-C₃)alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 8-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted
15 with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents,

a pharmaceutically acceptable salt thereof, a prodrug of the
20 compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

10. The compound of Claim 9 wherein R^3 is hydrogen, methyl or trifluoromethyl;

25 a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

11. The compound of Claim 9 wherein R^4 is a chemical moiety selected from the group consisting of (C₁-C₈)alkyl, aryl(C₁-C₄)alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), and 3- to 8-
30 membered partially or fully saturated carbocyclic ring(s), and 3- to 8-

membered partially or fully saturated heterocycle where said chemical moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

5

12. The compound of Claim 10 wherein R^4 is a chemical moiety selected from the group consisting of (C₁-C₈)alkyl, aryl(C₁-C₄)alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), and 3- to 8-membered partially or fully saturated heterocycle where said chemical moiety is optionally substituted with one or more substituents;

10

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

13. The compound of Claim 11 wherein R^4 is (C₁-C₈)alkyl, fluoro-substituted (C₁-C₈)alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl;

15

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

14. The compound of Claim 12 wherein R^4 is (C₁-C₈)alkyl, fluoro-substituted (C₁-C₈)alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl;

20

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

25

15. The compound of Claim 9, 10, 11, 12, 13, or 14 wherein R^{1a} is chloro, fluoro, cyano, or methyl; R^{1b} is chloro or fluoro; R^{2b} is chloro, fluoro, (C₁-C₄)alkyl, trifluoromethyl, (C₁-C₄)alkoxy, or cyano; m is 0 or 1; and n is 0;

30

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

16. A pharmaceutical composition comprising (1) a compound of any one of the preceding Claims, or a solvate or hydrate of said compound or said salt; and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

5

17. The composition of Claim 17 further comprising at least one additional pharmaceutical agent selected from a nicotine receptor partial agonist, an opioid antagonist, a dopaminergic agent, an attention deficit disorder agent, or an anti-obesity agent.

10

18. A method for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist in animals comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Claim 1 or 9, a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

15

19. The method of Claim 18 wherein said disease, condition or disorder modulated by a cannabinoid receptor antagonist is selected from the group consisting of eating disorders, weight loss or control, obesity, bulimia, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors, alcoholism, tobacco abuse, dementia, seizure disorders, epilepsy, attention deficit disorder, Parkinson's disease, inflammation, gastrointestinal disorders, and type II diabetes.

20

20. The use of a compound of Claim 1 or 9 in the manufacture of a medicament for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist.

30

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/IB2004/004019

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/4985 A61P25/00
 //(C07D487/04,239:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BARTH F: "Cannabinoid receptor agonists and antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 8, no. 3, March 1998 (1998-03), pages 301-313, XP002150850 ISSN: 1354-3776 page 302 - page 309</p> <p style="text-align: center;">-/-</p>	1-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *G* document member of the same patent family

Date of the actual completion of the international search

3 May 2005

Date of mailing of the international search report

20/05/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Goss, I

INTERNATIONAL SEARCH REPORT

Inter al Application No

PCT/IB2004/004019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STOIT A R ET AL: "DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF RIGID CANNABINOID CB RECEPTOR ANTAGONISTS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 50, no. 8, August 2002 (2002-08), pages 1109-1113, XP001181236 ISSN: 0009-2363 page 1109, right-hand column - page 1111, right-hand column, paragraph 2	1-20
A	GOYA P ET AL: "RECENT ADVANCES IN CANNABINOID RECEPTOR AGONISTS AND ANTAGONISTS" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 10, no. 10, 2000, pages 1529-1538, XP001036546 ISSN: 1354-3776 page 1530 - page 1536	1-20
A,P	US 2004/116328 A1 (YOSHIKAWA SEIJI ET AL) 17 June 2004 (2004-06-17) page 8, left-hand column, paragraph 156; compound (I)	1

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/IB2004/004019

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/004019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004116328 A1	17-06-2004	AU 2003241960 A1	22-12-2003
		BR 0311697 A	22-03-2005
		CA 2485641 A1	18-12-2003
		EP 1514552 A1	16-03-2005
		WO 03104229 A1	18-12-2003

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)